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TOXICOLOGY AND CARCINOGENESIS STUDIES OF BROMODICHLOROMETHANE

(CAS NO. 75-27-4)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

COMPLETED

ORIGINAL

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF BROMODICHLOROMETHANE

(CAS NO. 75-27-4)

IN F344/N RATS AND $B6C3F_1$ MICE

(GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

October 1987

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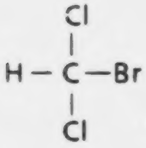
Public Health Service
National Institutes of Health

NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.



$$H-\overset{\displaystyle Cl}{\underset{\displaystyle Cl}{C}}-Br$$

BROMODICHLOROMETHANE

CAS No. 75-27-4

$CHBrCl_2$ Molecular weight 163.83

Synonym: Dichlorobromomethane

ABSTRACT

Bromodichloromethane (99% pure), one of several trihalomethanes commonly formed after chlorination of water, was selected for study because no carcinogenicity data were available for this compound and because chloroform, a related trihalomethane, had been found to cause tumors in rodents. The general population might be exposed to bromodichloromethane in drinking water supplies, in swimming pools, and in a variety of food substances.

Single-administration, 14-day, 13-week, and 2-year studies were conducted in F344/N rats and $B6C3F_1$ mice. The chemical was administered by gavage in corn oil because human exposure is primarily oral. Additional studies were performed to evaluate the potential for genetic damage in bacteria and mammalian cells.

Results of the Short-Term Studies: In the single-administration studies, the chemical was administered at doses of 150-2,500 mg/kg per day. All rats and female mice at 1,250 and 2,500 mg/kg and all male mice at 600, 1,250, and 2,500 mg/kg died; 2/5 male rats, 1/5 female rats, and 2/5 female mice at 600 mg/kg died; all animals at lower dose levels survived.

In the 14-day studies, rats received doses of 38-600 mg/kg, and mice received doses of 19-300 mg/kg per day. One female rat at 38 mg/kg and one female rat at 600 mg/kg died. Weight loss or decreased weight gain was seen at 300 and 600 mg/kg in male and female rats. All male mice at 150 and 300 mg/kg died, and one female mouse at 300 mg/kg died; no weight effects were observed in surviving mice. Dose-related necropsy findings included reddened renal medullae in male rats at 600 mg/kg and in male mice at 150 and 300 mg/kg. Clinical signs seen in high dose groups after dosing were hyperactivity in rats and lethargy in mice.

In the 13-week studies, male and female rats received doses of 19-300 mg/kg per day, male mice received doses of 6.25-100 mg/kg per day, and female mice received doses of 25-400 mg/kg per day. Five of 10 male rats and 2/10 female rats at 300 mg/kg died. None of the mice died. Final body weights of male and female rats at 150 and 300 mg/kg were lower than those of vehicle controls (45%-88% of vehicle control weights); final body weights of male mice at 100 mg/kg and female mice at 400 mg/kg were 92% and 94% of those of the vehicle controls. Centrilobular degeneration in the liver and degeneration and necrosis of the kidney were seen in male rats at 300 mg/kg; centrilobular degeneration was seen in female rats at 300 mg/kg; degeneration and necrosis of the kidney were seen in male mice at 100 mg/kg, and centrilobular degeneration of the liver was seen in female mice at 200 and 400 mg/kg.

Experimental Design of the Two-Year Studies: The 2-year toxicology and carcinogenesis studies of bromodichloromethane were conducted by administering the chemical in corn oil by gavage, 5 days per week for 102 weeks, to groups of 50 male and female rats at doses of 0, 50, or 100 mg/kg per day; to groups of 50 male mice at doses of 0, 25, or 50 mg/kg per day; and to groups of 50 female mice at doses of 0, 75, or 150 mg/kg per day. The study in male rats was restarted because at 10.5 months into the original study, a temperature elevation killed 45/50 vehicle control male rats.

Survival and Body Weight in the Two-Year Studies: Final survival of dosed rats was comparable to that of vehicle controls (male: vehicle control, 28/50; low dose, 36/50; high dose, 28/50; female: 34/50; 27/50; 41/50). Mean body weights of high dose male and female rats were decreased during the last 1.5 years of the study; final mean body weights of high dose male and female rats were 88% and 79% of vehicle control mean weights. Final mean body weights of low dose male and female rats were comparable to those of the vehicle controls.

Final survival of dosed male mice was comparable to that of the vehicle controls (34/50; 32/50; 42/50). At week 84, survival of female mice was greater than 50% in all dose groups. After week 84, survival of dosed and vehicle control female mice was reduced (final survival: 26/50; 13/50; 15/50), and this decreased survival was associated with ovarian abscesses (8/50; 19/47; 18/49). The final mean body weight of high dose male mice was 95% that of the vehicle controls; the final mean body weight of low dose male mice was comparable to that of the vehicle controls. Mean body weights of high dose female mice were decreased during the last 1.5 years of the study; the final mean body weight was 75% that of vehicle controls. The final mean body weight of low dose female mice was 91% that of vehicle controls.

Nonneoplastic Effects in the Two-Year Studies. Compound-related nonneoplastic lesions included cytomegaly and tubular cell hyperplasia of the kidney and necrosis and fatty metamorphosis of the liver in male rats; eosinophilic cytoplasmic change, clear cell change, focal cellular change, and fatty metamorphosis of the liver and tubular cell hyperplasia of the kidney in female rats; fatty metamorphosis of the liver, renal cytomegaly, and follicular cell hyperplasia of the thyroid gland in male mice; and follicular cell hyperplasia of the thyroid gland in female mice.

Neoplastic Effects in the Two-Year Studies: Bromodichloromethane caused compound-related increases in the incidences of neoplasms of the large intestine and kidney in male and female rats, the kidney in male mice, and the liver in female mice, as shown in the facing table. The neoplasms of the large intestine and kidney are uncommon tumors in F344/N rats and B6C3F$_1$ mice.

Administration of bromodichloromethane was also associated with a decrease in tumors of the adrenal glands in male rats, the pituitary and mammary glands in female rats, and the pituitary gland in female mice.

Genetic Toxicology: Bromodichloromethane was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested by the preincubation protocol at concentrations of up to 1,000 µg/plate with or without metabolic activation. The compound was not mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the absence of S9 but did induce forward mutations in this system in the presence of metabolic activation from rat liver S9. Cytogenetic tests with Chinese hamster ovary cells demonstrated no induction of chromosomal aberrations or sister chromatid exchanges following treatment with bromodichloromethane in either the presence or absence of metabolic activation.

COMPOUND-RELATED INCREASED INCIDENCES OF NEOPLASMS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

RATS			
Male	**Vehicle Control**	**50 mg/kg**	**100 mg/kg**
Large intestine			
Adenomatous polyp	0/50	3/50	33/50
Adenocarcinoma	0/50	11/50	38/50
Kidney			
Tubular cell adenoma	0/50	1/50	3/50
Tubular cell adenocarcinoma	0/50	0/50	10/50
Female	**Vehicle Control**	**50 mg/kg**	**100 mg/kg**
Large intestine			
Adenomatous polyp	0/46	0/50	7/47
Adenocarcinoma	0/46	0/50	6/47
Kidney			
Tubular cell adenoma	0/50	1/50	6/50
Tubular cell adenocarcinoma	0/50	0/50	9/50
MICE			
Male	**Vehicle Control**	**25 mg/kg**	**50 mg/kg**
Kidney			
Tubular cell adenoma	1/49	2/50	6/50
Tubular cell adenocarcinoma	0/49	0/50	4/50
Female	**Vehicle Control**	**75 mg/kg**	**150 mg/kg**
Liver			
Hepatocellular adenoma	1/50	13/48	23/50
Hepatocellular carcinoma	2/50	5/48	10/50

Data Audit: An audit of the experimental data was conducted for the 2-year toxicology and carcinogenesis studies of bromodichloromethane. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity*[*] for male and female F344/N rats and B6C3F$_1$ mice as shown by increased incidences of tubular cell adenomas and adenocarcinomas in the kidney and adenocarcinomas and adenomatous polyps in the large intestine in male and female rats, increased incidences of tubular cell adenomas and adenocarcinomas in the kidney of male mice, and increased incidences of hepatocellular adenomas and carcinomas in female mice.

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[*] Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.

A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF BROMODICHLOROMETHANE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
50 or 100 mg/kg bromodichloromethane in corn oil, 5 d/wk	50 or 100 mg/kg bromodichloromethane in corn oil, 5 d/wk	25 or 50 mg/kg bromodichloromethane in corn oil, 5 d/wk	75 or 150 mg/kg bromodichloromethane in corn oil, 5 d/wk
Survival rates in the 2-year study			
28/50; 36/50; 23/50	34/50; 27/50; 41/50	34/50; 32/50; 42/50	26/50; 13/50; 15/50
Nonneoplastic effects			
Cytomegaly and tubular cell hyperplasia of the kidney and necrosis and fatty metamorphosis of the liver	Eosinophilic cytoplasmic change, clear cell change, focal cellular change, and fatty metamorphosis of the liver and tubular cell hyperplasia of the kidney	Fatty metamorphosis of the liver, renal cytomegaly, and follicular cell hyperplasia of the thyroid gland	Follicular cell hyperplasia of the thyroid gland
Neoplastic effects			
Renal tubular cell adenomas and adenocarcinomas, and adenomatous polyps and adenocarcinomas of the large intestine	Renal tubular cell adenomas and adenocarcinomas, and adenomatous polyps and adenocarcinomas of the large intestine	Renal tubular adenomas and adenocarcinomas	Hepatocellular adenomas and carcinomas
Level of evidence of carcinogenic activity			
Clear evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology			
Not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537; not mutagenic in mouse L5178Y lymphoma cells; did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans.

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

CONTENTS

PAGE

NOTE TO READER 2

ABSTRACT 3

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY 7

PEER REVIEW PANEL 10

SUMMARY OF PEER REVIEW COMMENTS 11

CONTRIBUTORS 12

I. INTRODUCTION 13

II. MATERIALS AND METHODS 19

- PROCUREMENT AND CHARACTERIZATION OF BROMODICHLOROMETHANE 20
- PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES 23
- SINGLE-ADMINISTRATION STUDIES 26
- FOURTEEN-DAY STUDIES 26
- THIRTEEN-WEEK STUDIES 26
- TWO-YEAR STUDIES 29
  - STUDY DESIGN 29
  - SOURCE AND SPECIFICATIONS OF ANIMALS 29
  - ANIMAL MAINTENANCE 30
  - CLINICAL EXAMINATIONS AND PATHOLOGY 30
  - STATISTICAL METHODS 31

III. RESULTS 33

- RATS 34
  - SINGLE-ADMINISTRATION STUDIES 34
  - FOURTEEN-DAY STUDIES 35
  - THIRTEEN-WEEK STUDIES 35
  - TWO-YEAR STUDIES 36
    - BODY WEIGHTS AND CLINICAL SIGNS 36
    - SURVIVAL 39
    - PATHOLOGY AND STATISTICAL ANALYSES OF RESULTS 41
- MICE 48
  - SINGLE ADMINISTRATION STUDIES 48
  - FOURTEEN-DAY STUDIES 48
  - THIRTEEN-WEEK STUDIES 49

CONTENTS (Continued)

PAGE

TWO-YEAR STUDIES 50

BODY WEIGHTS AND CLINICAL SIGNS 50

SURVIVAL 53

PATHOLOGY AND STATISTICAL ANALYSES OF RESULTS 53

IV. DISCUSSION AND CONCLUSIONS 59

V. REFERENCES 65

APPENDIXES

APPENDIX A SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE 73

APPENDIX B SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE 99

APPENDIX C SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE 121

APPENDIX D SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE 143

APPENDIX E GENETIC TOXICOLOGY OF BROMODICHLOROMETHANE 163

APPENDIX F SENTINEL ANIMAL PROGRAM 171

APPENDIX G INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 175

APPENDIX H DATA AUDIT SUMMARY 181

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on bromodichloromethane on August 19, 1986, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF BROMODICHLOROMETHANE

On August 19, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of bromodichloromethane received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Exp ts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J. Dunnick, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male and female rats and male and female mice).

Dr. Capen, a principal reviewer, agreed with the conclusions as written. He questioned the rationale for giving female mice threefold higher doses than male mice. Dr. Dunnick reported that the dose levels used derived from marked differences in mortality in short-term studies.

As a second principal reviewer, Dr. Chinchilli agreed with the conclusions. He said the experimental design appeared adequate but asked that more information on the randomization scheme be included in the report.

As a third principal reviewer, Dr. Perera also agreed with the conclusions. She said that the rationale for using corn oil gavage should be expanded because drinking water and microencapsulation were the exposure routes in studies by other investigators. Dr. Dunnick replied that the NCI/NTP studies with other trihalomethanes, chloroform, and chlorodibromomethane, were by corn oil gavage so the same route was chosen to allow more direct comparison of the results.

Other discussion centered on whether formal statistical analyses should be carried out for nonneoplastic lesions and whether results on these lesions, when deemed to be statistically and biologically significant, should be included in the abstract of the report. In particular, there was discussion as to whether the renal lesions in rats were similar to those observed in male rats exposed to other hydrocarbons. Dr. Popp stated it would be worthwhile to compare these lesions in the current studies with renal lesions induced by other halogenated hydrocarbons. Dr. Scala suggested that the findings with the trihalomethanes be summarized.

Dr. Capen moved that the Technical Report on bromodichloromethane be accepted with the conclusions as written for male and female rats and mice, clear evidence of carcinogenic activity. Dr. Perera seconded the motion, and it was approved unanimously with 10 affirmative votes.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Bromodichloromethane is based on 13-week studies that began in August 1979 and ended in November 1979 and on 2-year studies that began in June 1981 for male rats, July 1980 for female rats, and June 1980 for male and female mice and ended in June 1983 for male rats, July 1982 for female rats, and June 1982 for male and female mice at EG&G Mason Research Institute.

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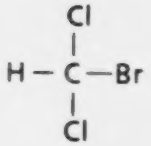
I. INTRODUCTION

Formation and Regulation
Toxicity in Animals
Studies of Chronic Toxicity
Metabolism and Distribution
Genetic Toxicology
Epidemiologic Studies
Study Rationale

I. INTRODUCTION



$$H-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-Br$$

BROMODICHLOROMETHANE

CAS No. 75-27-4

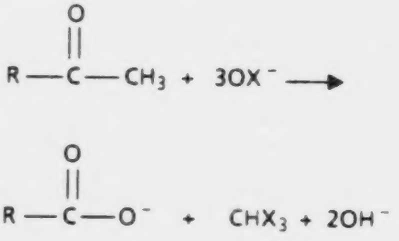
$CHBrCl_2$ Molecular weight 163.83

Synonym: Dichlorobromomethane

Formation and Regulation

Bromodichloromethane, a clear, colorless liquid with a density of 1.980 g/ml at 20° C, is one of several trihalomethanes formed when organic substances in water react with chlorine or bromine (Hoehn et al., 1978; Rook, 1980; Stevens et al., 1976; NAS, 1980a). The U.S. Environmental Protection Agency has established a maximum contamination level of 0.1 mg/liter for total trihalomethanes in community water systems serving more than 10,000 persons (USEPA, 1979, 1983a,b). The presence of trihalomethanes in drinking water is believed to pose a risk to humans because chloroform, another trihalomethane found in drinking water, was determined to be a carcinogen in rats and mice (NCI, 1976a; Eschenbrenner and Miller, 1945; Roe et al., 1979; IARC, 1979). The organic precursors of trihalomethanes are more frequently found in surface water than in ground water (USEPA, 1979). Trihalomethanes are widespread in the environment, not only in water supplies but also in swimming pools (Beech et al., 1980), soft drinks (Abdel-Rahman, 1982), baby bottles (Lahl et al., 1982), fish samples (Hiatt, 1983), and dump sites (Silkworth et al., 1984). The content of trihalomethanes in water increases with chlorination (Rook, 1974; Bellar et al., 1974; Brass et al., 1977; Symons et al., 1975). The mean concentration of bromodichloromethane in chlorinated water supplies in the United States is 0.017 mg/liter (range, 0-0.125 mg/liter) (USEPA, 1979). Assuming that the average daily water consumption for an adult male weighing 70 kg is 2 liters per day, intake of bromodichloromethane could reach a maximum daily consumption of 4.0 μg/kg per day (Balster and Borzelleca, 1982).

Bunn et al. (1975) have proposed the following model for the formation of trihalomethanes by the chlorination of organic material in surface water (where X = Cl, Br and/or I and R = organic material):



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-CH_3 + 3OX^- \longrightarrow$$

$$R-\overset{\overset{\displaystyle O}{\|}}{C}-O^- + CHX_3 + 2OH^-$$

Toxicity in Animals

The following oral LD_{50} values have been reported for bromodichloromethane: 450 mg/kg, male ICR mice; 900 mg/kg, female ICR mice; 916 mg/kg, male Sprague Dawley rats; 450 mg/kg, male CD-1 mice; 900 mg/kg, female CD-1 mice; and 969 mg/kg, female Sprague Dawley rats (Bowman et al., 1978; Borzelleca, 1983; Chu et al., 1982a). Clinical signs associated with bromodichloromethane administration at LD_{50} or higher doses included piloerection, sedation, flaccid muscle tone, ataxia, prostration, and enlargement and congestion of the liver and kidneys. Bromodichloromethane administered in corn oil by gavage for 14 consecutive days to 10 male CD-1 mice at 148 mg/kg per day caused liver and kidney damage, no effect on body weight gain was seen (Condie et al., 1983). Microscopic evaluation showed focal inflammation of the liver and intratubular mineralization and epithelial hyperplasia of the kidney. Kidney function was judged to be impaired because uptake of *p*-aminohippurate in renal cortical slices was decreased. No dose-related changes were seen in blood urea nitrogen and serum creatinine levels; serum glutamic-pyruvic transaminase activity (SGPT) was elevated. Acetone pretreatment (15 mmol/kg) has been shown to potentiate the hepatotoxicity of bromodichloromethane administered as a single oral dose in corn oil (1.0 ml/kg) to Sprague Dawley rats (Hewitt et al., 1983).

Munson et al. (1982) conducted a 14-day study in male and female CD-1 mice in which bromodichloromethane was administered by gavage in a solution of 10% emulphor at levels of 50-250 mg/kg per day. At the highest dose, liver weight, serum glutamic-oxaloacetic transaminase and SGPT activities, and blood urea nitrogen levels increased; body weight gain, serum glucose levels, and spleen weight decreased. Four days before being killed, a separate group of mice was immunized with sheep erythrocytes. The mice were killed, and spleen cell suspensions were prepared and assayed for antibody-forming cells; at 250 mg/kg, antibody-forming cells were decreased, suggesting impairment of the immune system. Histopathologic evaluation of tissues was not reported.

Bromodichloromethane administered to male and female Sprague Dawley rats for 90 days in drinking water at levels up to 2,500 ppm (resulting in doses of approximately 100 mg/kg body weight and 135 mg/kg body weight) produced mild toxicity in the liver and decreased body weight gain (Chu et al., 1982a,b). The vacuolar changes observed in the liver, interpreted as fatty infiltration, were reversed after a 90-day recovery period.

Bromodichloromethane was given to pregnant Sprague Dawley rats by gavage in corn oil on days 6-15 of gestation at doses of 0, 50, 100, or 200 mg/kg per day (Ruddick et al., 1983). At the highest doses, maternal body weight gain was decreased, but no teratogenic effects were observed. A mixture of trihalomethanes and other organic substances concentrated from water was given by gavage in dimethyl sulfoxide to pregnant CD-1 mice at 51, 170, or 510 mg/kg per day on days 7-14 of gestation; no indication of fetal toxicity was observed (Kavlock et al., 1979). By weight, the mixture contained 69% chloroform, 16% bromodichloromethane, 10% chlorodibromomethane, and 4% bromoform.

Studies of Chronic Toxicity

Bromodichloromethane or chloroform was administered in drinking water to male and female Wistar rats for up to 180 weeks (Tumasonis et al., 1985). During the first 72 weeks of the study, bromodichloromethane was administered at concentrations of 0 or 1.2 ml (2.4 g) per liter of drinking water; at week 72, the concentration was halved because of a gradual increase in water intake. The dose of bromodichloromethane is estimated at 150 mg/kg per day in female rats and 200 mg/kg per day in male rats. Chloroform was administered at 0 or 2 ml (3 g) per liter drinking water (the concentration was halved after week 72). The liver and grossly observable lesions were examined. An increased incidence of hepatic neoplastic nodules was found in female rats (but not in male rats) when bromodichloromethane or chloroform was administered throughout the lifespan of the rat. The incidence of neoplastic nodules after bromodichloromethane administration was as follows: male rats--control, 5/22; dosed, 6/47; female rats--0/18; 17/53.

Bromodichloromethane was administered as a microencapsulated preparation in feed to Wistar rats at concentrations of 0, 140, 550, or 2,200 ppm (w/w) bromodichloromethane for 24 months. Histologic findings included cholangiofibrosis and/or fibrosis in the liver of males and females in the 2,200-ppm dose group at 6, 12, 18, and 24 months. Tumors of the liver were observed in dosed rats but not in control rats (M. Tobe, National Institute of Hygienic Sciences, Tokyo, Japan, personal communication to J. Dunnick, NTP, 1985).

Metabolism and Distribution

Bromodichloromethane was administered in corn oil by gavage to male Sprague Dawley rats at 100 mg/kg (16 µCi/kg) and to male $B6C3F_1$ mice at 150 mg/kg (32 µCi/kg) (Mink et al., 1986). Urine and expired gas were monitored for radioactivity, tissue distribution was determined. Eight hours after administration of bromodichloromethane, the percentage of radioactivity recovered as expired carbon dioxide was 14% in rats and 81% in mice; the percentage of unmetabolized compound in expired air was 41% in rats and 7% in mice. The percentage of recovered label at 8 hours in expired air, urine, and tissues was 63% for rats and 93% for mice. Radioactivity was found in the liver, kidney, and stomach. (Distribution to the colon and rectum and the dose per milligram of tissue were not reported.) These studies indicate that mice metabolize bromodichloromethane at a faster rate than do rats. Similar studies with chloroform, chlorodibromomethane, and bromoform indicated that mice also metabolize these trihalomethanes at a faster rate than do rats (Mink et al., 1986).

In another series of experiments, bromodichloromethane, chloroform, chlorodibromomethane, bromoform, and iodoform were administered intraperitoneally in corn oil to male Sprague Dawley rats at 1 mmol/kg body weight, blood samples were collected from the tail vein and the amount of total carbon monoxide was measured. The highest blood carbon monoxide levels were observed after iodoform and bromoform administration. chlorodibromomethane, bromodichloromethane, and chloroform were metabolized at slower rates (Anders et al., 1978).

In vitro studies with rat microsomal preparations demonstrate that trihalomethanes can be metabolized to carbon monoxide by hepatic microsomal mixed function oxidases. The authors hypothesize that the trihalomethanes, like chloroform, are metabolized to a phosgene-like intermediate, although this intermediate has not been isolated for bromoform, chlorodibromomethane, or bromodichloromethane (Stevens and Anders, 1979; Ahmed et al., 1977).

Genetic Toxicology

Bromodichloromethane at doses of 25-250 µl was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 with and without metabolic activation when exposure to the chemical occurred for a 7-10 hour period within the sealed environment of a desiccator (Simmon et al., 1977; Simmon, 1978; Simmon and Tardiff, 1978; Simmon and Kauhanen, 1978). Simmon et al. (1977) also reported a mutagenic effect in *Escherichia coli* strain WP2 exposed to bromodichloromethane in a desiccator by using this same treatment protocol with and without metabolic activation. However, in tests by these same investigators, bromodichloromethane was not mutagenic after exposure at up to 5,000 µg/ml in the standard Salmonella/microsome plate incorporation assay of Ames et al. (1975) with strains TA100, TA1535, TA1537, TA1538, or TA98 with or without metabolic activation. The chemical also was not mutagenic when tested by the NTP at doses up to 1,000 µg/plate in a 30-minute preincubation protocol with strains TA100, TA1535, TA1537, or TA98 with or without metabolic activation from Aroclor 1254-induced male Sprague Dawley rat and Syrian hamster liver S9 (Mortelmans et al., 1986; Appendix E, Table E1).

Bromodichloromethane did not induce mitotic recombination in the presence or absence of S9 in studies with *Saccharomyces cerevisiae* strain D3 treated in suspension (Simmon and Kauhanen, 1978). However, recent studies by Nestmann and Lee (1985) revealed weak effects in *S. cerevisiae* strains D7 and XV185-14C after exposure to bromodichloromethane in the absence of exogenous metabolic activation. The authors defined these responses as "weak" because the increase in the frequency of mitotic crossing-over did not exceed twice that of the controls, and the incidence of such events was not clearly related to the dose of bromodichloromethane.

Bromodichloromethane, when tested by the NTP in the L5178Y mouse lymphoma cell assay, induced forward mutations at the TK locus in the presence of S9 from the liver of Aroclor 1254-induced male F344 rats. Bromodichloromethane was not mutagenic to mouse lymphoma cells in the absence of exogenous metabolic activation; the number of mutants increased with increasing dose, but no single value for mutation frequency was significant at the $P<0.05$ level (Table F2).

In NTP-sponsored in vitro cytogenetics tests with Chinese hamster ovary cells, bromodichloromethane at doses of up to 5,000 µg/ml did not significantly increase the frequency of chromosomal aberrations or sister chromatid exchanges (SCEs) in either the presence or absence of S9 from Aroclor 1254-induced male Sprague Dawley rat liver; however, results of the second of two trials for induction of SCEs in the presence of S9 activation were considered questionable (Tables E3 and E4). Morimoto and Koizumi (1983) reported that bromodichloromethane produced a significant increase in the frequency of SCEs in both cultured human peripheral blood lymphocytes treated in vitro and in mouse bone marrow cells treated in vivo. The in vitro tests with human lymphocytes demonstrated dose-related increases in SCEs after a 72-hour exposure, with the highest dose (0.01 M, or approximately 1,640 µg/ml) producing a 60% increase in SCEs per cell over the solvent controls. In the in vivo studies, oral administration of bromodichloromethane in olive oil at doses of 25, 50, or 100 mg/kg per day for 4 days increased the frequency of SCEs in bone marrow cells of male ICR mice from less than six SCEs per cell in the vehicle controls to just over seven SCEs per cell in the 50 mg/kg group ($P<0.05$) and to just under eight SCEs per cell in the 100 mg/kg group ($P<0.01$). No increase in SCEs was observed in the 25 mg/kg group. Doses above 100 mg/kg per day killed all of the animals.

Three other trihalomethanes tested by Morimoto and Koizumi (1983) (chloroform, chlorodibromomethane, and bromoform) also induced SCEs in cultured human lymphocytes and mouse bone marrow cells in vivo. The relative mutagenic potential of all four trihalomethanes, as measured by their ability to induce SCEs, was directly proportional to the number of bromine atoms contained in the compound. Although Simmon et al. (1977) also obtained positive results with these same trihalomethanes in *S. typhimurium* after exposure in a desiccator, the magnitude of the effect was not related to the number of bromine atoms. In Salmonella, the greatest response was produced by chlorodibromomethane and the weakest response by bromoform.

Epidemiologic Studies

Epidemiologic studies have investigated the association between the effects of drinking chlorinated water containing various organic contaminants, including the trihalomethanes. These studies have looked at the risks for cancer of the urinary bladder, colon, and rectum (Cantor et al., 1978, 1985; Cantor, 1982, 1983; Lawrence et al., 1984; Cragle et al., 1985). Although some of these studies have suggested an association between these cancers and trihalomethane consumption, others have not. Reviews of epidemiologic studies (IARC, 1979, 1982; NAS, 1980a,b; Crump and Guess, 1982; Craun, 1985) indicate that final interpretation concerning the causal association must await completion of ongoing studies.

Study Rationale

Bromodichloromethane was studied because a related trihalomethane, chloroform (trichloromethane), had been found to be a carcinogen in rodents and because no data were available on the carcinogenicity of the other trihalomethanes at the time these studies were started. In addition to bromodichloromethane, tribromomethane (bromoform) and chlorodibromomethane were studied by the NTP in 2-year gavage studies in F344/N rats and $B6C3F_1$ mice. The oral route of administration was chosen for the present studies because human exposure is primarily oral. In the NCI/NTP studies, the trihalomethanes were administered in corn oil by gavage because these compounds are not soluble in water at the concentrations used.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BROMODICHLOROMETHANE
PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES
SINGLE-ADMINISTRATION STUDIES
FOURTEEN-DAY STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES
    Study Design
    Source and Specifications of Animals
    Animal Maintenance
    Clinical Examinations and Pathology
    Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF BROMODICHLOROMETHANE

Bromodichloromethane was obtained in three lots from PCR Research Chemicals, Inc. (Table 1). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). (MRI reports on the analyses performed in support of the bromodichloromethane studies are on file at NIEHS.)

All lots of the study chemical were identified as bromodichloromethane by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Infrared and nuclear magnetic resonance spectra were consistent with the structure and with literature spectra (representative spectra presented in Figures 1 and 2). The ultraviolet/visible spectrum was consistent with the structure of bromodichloromethane; no absorbance was found in the visible region.

Purity for all lots studied was determined by elemental analysis, Karl Fischer water analysis, titration of acidic components with sodium hydroxide, and gas chromatography. Gas chromatographic analysis was performed with flame ionization detection and either a 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport packed column (system 1) or a 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW) packed column (system 2). Each batch of study material was purified to remove excess acid to enhance the long-term stability of the bulk material. Batches 01 and 02 of lot no. 1257 were purified by shaking with aqueous sodium carbonate solution, drying with anhydrous magnesium sulfate, and treating with deactivated charcoal. All subsequent batches were purified by column chromatography with deactivated Woelm Basic Alumina. Results of the purity analyses are presented in Table 2.

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF BROMODICHLOROMETHANE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Number			
1257 (batch 01)	1257 (batch 01)	1257 (batch 02)	1257 (batches 02 and 03), 1250 (batch 04), and 1251
Date of Initial Use			
12/13/78	3/28/79	8/13/79	Lot no. 1257 (batch 02)--6/17/80; 1257 (batch 03)--6/18/81; 1250 (batch 04)--11/12/81; 1251--12/23/82
Supplier			
PCR Research Chemicals, Inc. (Gainesville, FL)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

TABLE 2. RESULTS OF PURITY ANALYSES OF BROMODICHLOROMETHANE

Lot No.	Determined Purity (percent)	Percent Water	Acid Content After Purification (ppm)	Total Impurities (percent)	
				System 1	System 2
1257 (batch 01)	~ 99	0.03	9	0.39	0.44
1257 (batch 02)	> 99	0.01	6	0.44	0.36
1257 (batch 03)	> 99	< 0.01	< 5	0.35	0.29
1250	> 99	< 0.05	7.5	0.29	0.33
1251	~ 99	< 0.05	< 25	0.98	0.95

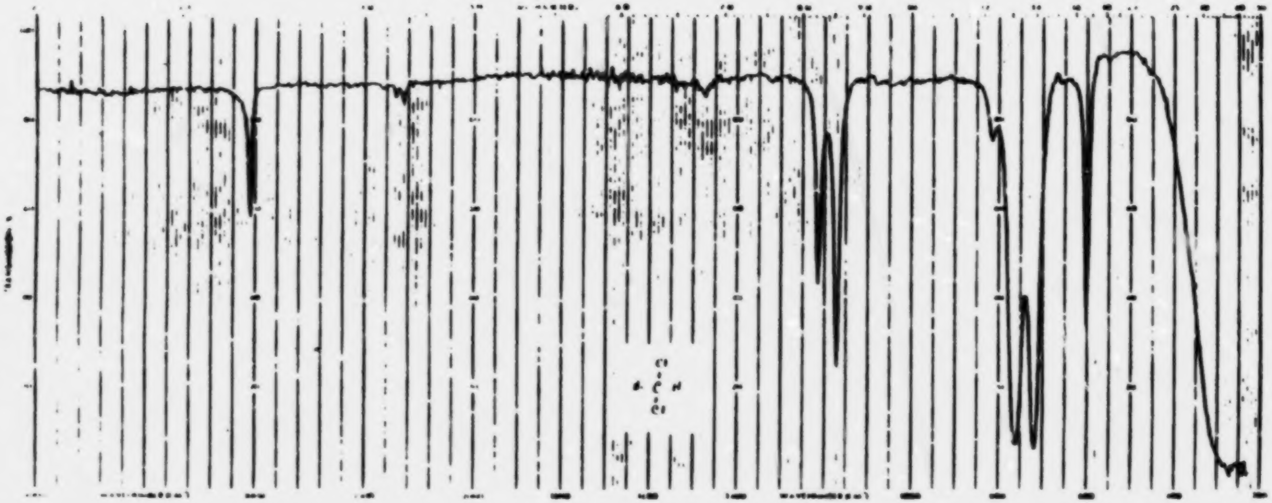


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF BROMODICHLOROMETHANE
(LOT NO. 1[illegible]7, BATCH 03)

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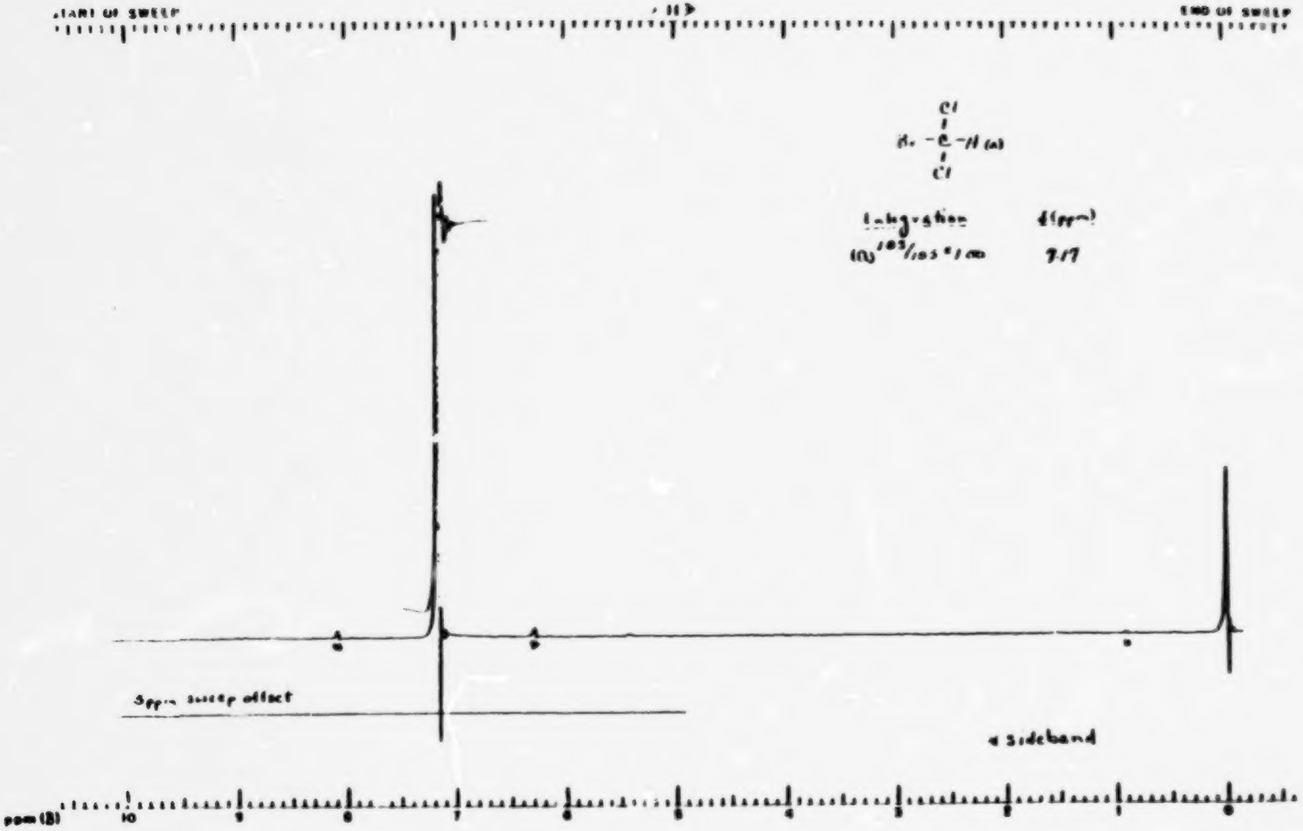

FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF BROMODICHLOROMETHANE (LOT NO. 1257, BATCH 03)

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Stability studies performed by gas chromatography with the same column as that described above for system 2 indicated that bromodichloromethane was stable as a bulk chemical when kept for 2 weeks at temperatures of up to 60° C. Due to the formation of free acid, the bromodichloromethane study material was passed through an alumina column each month before use at the beginning of the 2-year studies. Approximately 60 ml of the bulk chemical was percolated through a 1.5 cm × 15 cm bed of Woelm Basic Alumina in a glass chromatographic column with a Teflon® stopcock. The eluate was collected in an amber bottle preflushed with dry nitrogen. After July 1981, bromodichloromethane was passed through an alumina column only if the acid content was determined to be over 500 ppm after bulk reanalysis. During the 13-week and 2-year studies, bromodichloromethane was stored at lower than 0° C. Confirmation of the stability of the bulk chemical during the toxicity and carcinogenic activity studies was obtained by titration for free acid and by gas chromatographic analysis with the same column as that described above for system 1. No deterioration of the study material was seen over the course of the studies. Identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

The appropriate amounts of bromodichloromethane and corn oil were mixed (w/v) to give the desired concentrations (Table 3). The stability of bromodichloromethane in corn oil (10% concentration) was determined by gas chromatography with system 2 after extraction with methanol containing 0.5506 mg/ml *n*-amyl alcohol as an internal reference. The chemical in corn oil was found to be stable for at least 7 days at room temperature. During the 13-week studies, bromodichloromethane/corn oil mixtures were stored under a nitrogen atmosphere at 4° C for no longer than 2 weeks. During the 2-year studies, the dose mixtures were stored under an inert atmosphere at 0° ± 5° C for no longer than 10 days.

TABLE 3. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF BROMODICHLOROMETHANE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
Appropriate amounts of bromodichloromethane diluted with 50 ml corn oil in serum vials	Appropriate amounts of bromodichloromethane diluted with corn oil	Appropriate amounts of bromodichloromethane and corn oil mixed in ground glass-stoppered, graduated cylinders by inversion until visually uniform	Same as 13-wk studies
Maximum Storage Time			
	2 wk	2 wk	10 d
Storage Conditions			
4° C	4° C under nitrogen	4° C under nitrogen	0° ± 5° C, flushed with nitrogen and sealed in amber vials; after 5/14/81, flushed with argon and daily doses put in individual vials

Periodic analysis of formulated bromodichloromethane/corn oil dose mixtures was conducted at the study laboratory and the analytical chemistry laboratory by extraction of the dose mixtures with methanol containing 0.2 mg/ml *n*-amyl alcohol as an internal standard followed by gas chromatographic analysis of the resultant extract with system 2. Dose mixtures were analyzed three times during the 13-week studies. The results of the analysis of the first two mixes ranged from 166% to 17% of the target concentration. A problem with the mixing procedure was identified. The results of the third set of dose mixtures submitted for analysis (105%-90% of target) indicated that the revised formulation procedure was adequate (Table 4).

TABLE 4. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BROMODICHLOROMETHANE

Date Mixed	Concentration of Bromodichloromethane in Corn Oil (mg/ml)		Determined as a Percent of Target
	Target	Determined	
08/14/79	1.3	(c) 1.22	94
	2.5	(a) 2.08	(b) 83
	3.8	(a) 0.71	(b) 19
	5.0	(c) 5.00	100
	7.5	(c) 12.25	(b) 163
	10.0	(c) 7.50	(b) 75
	15.0	(c) 14.00	93
	20.0	(c) 12.25	(b) 61
	30.0	(c) 25.75	(b) 86
	40.0	(c) 65.00	(b) 163
	60.0	(c) 59.50	99
	80.0	(c) 77.75	97
08/23/79	2.5	(a) 2.94	(d) 118
	3.8	(a) 0.63	(d) 17
	7.5	(a) 12.50	(d) 166
	10.0	(a) 9.00	(e) 90
	20.0	(a) 18.00	(e) 90
	30.0	(a) 27.00	(e) 90
	40.0	(a) 39.00	(e) 98
09/13/79	1.3	(a) 1.34	103
	2.5	(a) 2.67	107
	3.8	(a) 3.86	102
	5.0	(a) 4.99	100
	7.5	(a) 8.00	107
	10.0	(c) 9.35	94
	15.0	(c) 14.50	97
	20.0	(c) 18.00	90
	30.0	(c) 30.50	102
	40.0	(c) 42.00	105
	60.0	(c) 61.00	102
	80.0	(c) 78.50	98

(a) Result of single analysis
(b) Out of specifications
(c) Result of duplicate analysis
(d) Remix; out of specifications.
(e) Remix

During the 2-year studies, the dose preparations were analyzed at approximately 8-week intervals. The mixtures were formulated within ±10% of the target concentrations approximately 96% (76/79) of the time throughout the studies (Table 5). Of the three dose formulations determined to be out of specifications, one was found to be 148% of the target concentration, and the other two were within ±16% of the target concentration. Referee analyses were periodically performed by the analytical chemistry laboratory. Generally good agreement was found between laboratories (Table 6).

TABLE 5. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

Date Mixed	Concentration of Bromodichloromethane in Corn Oil for Target Concentration (mg/ml) (a) 5	10	15	20	30
07/17/80	4.5	(b) 8.5	13.9	18.0	28.3
07/22/80	--	(c) 9.2	--	--	--
08/21/80	(b) 7.4	9.2	14.2	18.5	28.6
08/25/80	(c) 4.5	--	--	--	--
11/20/80	4.5	9.3	16.1	18.9	30.2
12/18/80	4.8	9.7	14.1	18.5	30.0
02/12/81	4.8	9.5	14.7	18.8	29.2
04/16/81	5.0	9.5	15.5	19.5	30.5
06/25/81	4.5	10.0	14.9	20.1	29.0
07/23/81	5.6	9.5	14.4	18.9	28.5
09/17/81	4.8	9.9	14.8	19.7	29.4
11/19/81	(b) 5.8	9.7	14.5	19.3	29.5
11/23/81	(c) 4.9	--	--	--	--
02/18/82	5.1	9.9	14.8	19.8	30.5
02/25/82	4.9	9.7	14.2	19.0	29.3
04/29/82	4.9	9.7	14.6	19.7	29.8
06/17/82	--	9.8	--	19.7	--
08/12/82	--	10.1	--	20.8	--
09/16/82	--	10.2	--	20.8	--
10/21/82	--	10.5	--	20.7	--
01/06/83	--	9.7	--	20.0	--
03/10/83	--	10.0	--	19.8	--
04/21/83	--	9.9	--	19.6	--
Mean (mg/ml)	5.1	9.7	14.7	19.5	29.1
Standard deviation	0.79	0.42	0.60	0.78	1.32
Coefficient of variation (percent)	15.5	4.3	4.1	4.0	4.5
Range (mg/ml)	4.5-7.4	8.5-10.5	13.9-16.1	18.0-20.8	25.5-30.5
Number of samples	13	20	13	20	13

(a) Results of duplicate analysis
(b) Out of specifications; not used in the study.
(c) Remix; not included in the mean.

TABLE 6. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

Date Mixed	Lot No.	Target Concentration (mg/ml)	Determined Concentration (mg/ml) Study Laboratory (a)	Determined Concentration (mg/ml) Referee Laboratory (b)
08/21/80	1257 (batch 02)	10	9.2	10.4
02/12/81	1257 (batch 02)	30	29.2	30.5
09/17/81	1257 (batch 03)	15	14.8	15.7
02/18/82	1250	5	5.1	5.0
09/16/82	1250	20	20.8	19.9
03/10/83	1251	10	10.0	10.0

(a) Results of duplicate analysis
(b) Results of triplicate analysis

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 19 days before the studies began.

Groups of five rats and five mice of each sex were administered a single dose of 150, 300, 600, 1,250, or 2,500 mg/kg bromodichloromethane in corn oil by gavage. Animals were observed once per hour for 3 hours after dosing and then twice per day for 14 days. A necropsy was performed on at least one animal of each sex and dose group. Details of animal maintenance are presented in Table 7.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 15 days (rats) or 13 days (mice) before the studies began. The rats were approximately 6 weeks old and the mice 7 weeks old when placed on study.

Groups of five rats of each sex were administered 0, 38, 75, 150, 300, or 600 mg/kg bromodichloromethane in corn oil by gavage for 14 consecutive days. Groups of five mice of each sex were administered 0, 19, 38, 75, 150, or 300 mg/kg on the same schedule.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed twice per day and were weighed on days 0 and 14 and at the end of the studies. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 7.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of bromodichloromethane and to determine the doses to be used in the 2-year studies.

Four-week-old male and female F344/N rats and 5- to 7-week old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 21 days, and then assigned to dose groups so that the average cage weights were approximately equal for all animals of the same sex and species. Rats were approximately 7 weeks old and mice 8-10 weeks old when placed on study.

Groups of 10 rats of each sex were administered 0, 19, 38, 75, 150, or 300 mg/kg bromodichloromethane in corn oil by gavage, 5 days per week for 13 weeks. (The 19 mg/kg group of rats was administered 1.9 mg/kg for the first 3 weeks of the studies.) Groups of 10 male mice were administered 0, 6.25, 12.5, 25, 50, or 100 mg/kg; and groups of female mice were administered 0, 25, 50, 100, 200, or 400 mg/kg on the same schedule.

TABLE 7. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BROMODICHLOROMETHANE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
150, 300, 600, 1,250, or 2,500 mg/kg bromodichloromethane in corn oil by gavage; dose vol--5 ml/kg	Rats--0, 38, 75, 150, 300, or 600 mg/kg bromodichloromethane in corn oil by gavage; mice--0, 19, 38, 75, 150, or 300 mg/kg; dose vol--5 ml/kg	Rats--0, 19, 38, 75 150, or 300 mg/kg bromodichloromethane in corn oil by gavage (the 19 mg/kg group received 1.9 mg/kg for the first 3 wk); mice--male: 0, 6.25, 12.5, 25, 50, or 100 mg/kg; female: 0, 25, 50, 100, 200, or 400 mg/kg; dose vol--5 ml/kg	Rats--0, 50, or 100 mg/kg bromodichloromethane in corn oil by gavage; mice--male: 0, 25, or 50 mg/kg; female: 0, 75, or 150 mg/kg; dose vol--5 ml/kg
Date of First Dose			
12/13/78	3/28/79	8/13/79	Rats--male: 6/1/81; female: 7/8/80; mice--6/18/80
Date of Last Dose			
N/A	4/11/79	11/12/79	Rats--male: 5/14/83; female: 6/28/82; mice--6/6/82
Duration of Dosing			
Single dose only	14 consecutive d	5 d/wk for 13 wk	5 d/wk for 102 wk
Type and Frequency of Observation			
Animals observed 1 × h for 3 h after dosing, then 2 × d; animals weighed before dosing and on d 2	Observed 2 × d; weighed on d 0, 14, and at the end of the studies	Clinical observations 2 × d; weighed 1 × wk	Observed 2 × d; weighed 1 × wk for 12 wk, 1 × 4 wk thereafter
Necropsy and Histologic Examination			
Necropsy performed on at least one animal of each sex and dose group	Necropsy performed on all animals; histologic exam not performed	Necropsy performed on all animals. Histologic exam performed on vehicle controls and 150 and 300 mg/kg groups of rats and vehicle controls and 50, 100, 200, and 400 mg/kg groups of mice. The following tissues examined histologically: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gross lesions, heart, liver, lungs and bronchi, mammary gland, mandibular lymph nodes, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, salivary gland, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae, stomach, thymus, thyroid gland, tissue masses, trachea, and urinary bladder.	Necropsy performed on all animals. Histologic exam performed on all vehicle control and high dose male rats, all female rats, and all male and female mice. The following tissues examined: adrenal glands, bone marrow, brain, colon, costochondral junction, duodenum, esophagus, gallbladder (mice), heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroids, pituitary gland, preputial gland, prostate/testes/seminal vesicles or ovaries/uterus, salivary gland, skin, spleen, stomach, thigh muscle, thymus, thyroid gland, tissue masses and abnormal regional lymph nodes, trachea, and urinary bladder. The following tissues were examined histologically for low dose male rats: adrenal glands, colon, heart, kidney, liver, lung, pancreas, preputial gland, and rectum.

TABLE 7. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BROMODICHLOROMETHANE (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Study Laboratory			
EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute
Method of Animal Identification			
Ear punch	Ear punch	Ear punch	Ear punch
Time Held Before Study			
19 d	Rats--15 d; mice--13 d	21 d	Rats--male: 23 d; female: 19 d; mice--14 d
Age When Placed on Study			
6 wk	6-7 wk	Rats--7 wk; mice--8-10 wk	8 wk
Age When Killed			
8 wk	8-10 wk	Rats--20-21 wk; mice--21-24 wk	112-113 wk
Necropsy Dates			
12/28/78	Rats--4/15/79-4/17/79; mice--4/13/79-4/16/79	Rats--11/14/79-11/21/79; mice--11/13/79-11/16/79	Rats--male: 5/31/83-6/5/83; female: 7/7/82-7/14/82; mice--6/16/82-6/22/82
Method of Animal Distribution			
Randomized by weight so that all cage weights were approximately equal	Same as single-administration studies	Same as single-administration studies	Assigned to cages according to a table of random numbers; cages assigned to groups by a table of random numbers
Feed			
Wayne Lab meal (Allied Mills, Inc., Chicago, IL); available ad libitum	Wayne Lab Blox (Allied Mills, Inc., Chicago, IL); available ad libitum	Same as 14-d studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum
Bedding			
Aspen Bed® (American Excelsior Co., Baltimore, MD)	Same as single-administration studies	Aspen Bed® (American Excelsior Co., Baltimore, MD) or Beta Chips® (Agway Inc., Syracuse, NY)	Aspen Bed® (American Excelsior Co., Baltimore, MD)
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages			
Polycarbonate (Lab Products, Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cage Filters			
Nonwoven fiber filters (Lab Products)	Same as single-administration studies	Nonwoven fiber filters (Lab Products, Rochelle Park, NJ)	Nonwoven fiber filters (Lab Products or Snow Filtration, Cincinnati, OH)

TABLE 7. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF BROMODICHLOROMETHANE (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--20.6°-22.2° C; hum--17%-49%; fluorescent light 12 h/d; 10 room air changes/h	Temp--17.2°-26.1° C; hum--20%-52%; fluorescent light 12 h/d; 10 room air changes/h	Temp--18.3°-27.2° C, average 21.8° C; hum--28%-70%, average 48%; fluorescent light 12 h/d; 10-12 room air changes/h	(a) Male rats--temp: 20°-27° C; hum: 13%-78%; mice and female rats--temp: 21.1°-32.2° C (mean, 24.9° C); hum: 18%-78% (mean, 51%); fluorescent light 12 h/d; 12 room air changes/h

(a) Rats and mice were exposed to temperatures in excess of 32° C (89.6° F) on 4/24/81-4/25/81. Forty-five vehicle control male rats died; therefore, the male rat study was restarted in a separate room. The restarted study is the one described in this report.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 7.

Animals were checked twice daily; moribund animals were killed. Individual animal weights were recorded weekly.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 7.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 50, or 100 mg/kg bromodichloromethane in corn oil by gavage, 5 days per week for 102 weeks. Groups of 50 male mice were administered 0, 25, or 50 mg/kg; and groups of 50 female mice were administered 0, 75, or 150 mg/kg on the same schedule. The studies in male rats were restarted because at 10.5 months into the original study, 45/50 vehicle control male rats died after the temperature in the animal room exceeded 32° C.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Male rats were shipped to the study laboratory at 5 weeks of age, female rats at 4-5 weeks of age, and mice at 5-6 weeks of age. The animals were quarantined at the study laboratory for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Neither the cages or racks were rotated during this study. Vehicle control animals were housed on the top two levels of the racks, low dose animals on the middle two levels, and high dose animals on the lower two levels. Further details of animal maintenance are given in Table 7.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on all dosed and vehicle control mice and female rats. For male rats, histopathologic examination of tissues was performed according to the "inverse pyramid" design (McConnell, 1983a,b). Complete histopathologic examinations (Table 7) were performed on high dose and vehicle control male rats and on all male rats dying early in the studies, including those in lower dose groups. In addition, histopathologic examinations were performed on all gross lesions and tissues/organs from male rats in the lower dose groups when chemically related neoplastic or nonneoplastic effects were identified in the high dose male rats.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as theratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the studies were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the studies, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the studies were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

- **SINGLE-ADMINISTRATION STUDIES**
- **FOURTEEN-DAY STUDIES**
- **THIRTEEN-WEEK STUDIES**
- **TWO-YEAR STUDIES**
  - **Body Weights and Clinical Signs**
  - **Survival**
  - **Pathology and Statistical Analyses of Results**

MICE

- **SINGLE-ADMINISTRATION STUDIES**
- **FOURTEEN-DAY STUDIES**
- **THIRTEEN-WEEK STUDIES**
- **TWO-YEAR STUDIES**
  - **Body Weights and Clinical Signs**
  - **Survival**
  - **Pathology and Statistical Analyses of Results**

SINGLE-ADMINISTRATION STUDIES

All rats that received 1,250 or 2,500 mg/kg bromodichloromethane and 2/5 males and 1/5 females that received 600 mg/kg died before the end of the studies (Table 8). Lethargy and labored breathing were observed for rats that received 1,250 or 2,500 mg/kg. At necropsy, the liver appeared pale in the 1,250 and 2,500 mg/kg groups. No dose-related weight effects were seen in animals surviving to the end of the 14-day observation period. The high dose selected for the 14-day studies was 600 mg/kg because all animals in the single-administration studies that received 1,250 and 2,500 mg/kg died.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF BROMODICHLOROMETHANE

		Mean Body Weights (grams)		
Dose (mg/kg)	Survival (a)	Initial (b)	Final	Change (c)
MALE (d)				
150	5/5	152 ± 4	207 ± 2	+55 ± 3
300	5/5	152 ± 4	202 ± 3	+50 ± 3
600	(e) 3/5	152 ± 4	212 ± 4	+62 ± 2
1,250	(f) 0/5	153 ± 4	(g)	(g)
2,500	(h) 0/5	153 ± 3	(g)	(g)
FEMALE (i)				
150	5/5	129 ± 3	157 ± 3	+28 ± 1
300	5/5	129 ± 3	154 ± 4	+25 ± 1
600	(j) 4/5	129 ± 3	152 ± 2	+23 ± 5
1,250	(k) 0/5	129 ± 3	(g)	(g)
2,500	(l) 0/5	130 ± 3	(g)	(g)

(a) Number surviving/number initially in group.
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) LD_{50} value of 651 mg/kg with a 95% confidence interval of 462-917 mg/kg; LD_{50} values by the Spearman-Karber method.
(e) Day of death: 4,8
(f) Day of death: 2,2,4,4,4
(g) No data are reported due to the 100% mortality in this group.
(h) Day of death: 1,1,1,1,4
(i) LD_{50} value of 751 mg/kg with a 95% confidence interval of 568-993 mg/kg; LD_{50} values by the Spearman-Karber method.
(j) Day of death: 6
(k) Day of death: 4,4,4,6,6
(l) Day of death: 3,3,3,4,4

FOURTEEN-DAY STUDIES

One of five female rats that received 38 mg/kg bromodichloromethane and 1/5 female rats that received 600 mg/kg died before the end of the studies (Table 9). All rats that received 600 mg/kg were hyperactive after they were dosed. Rats that received 600 mg/kg lost weight or gained no weight during the studies. Final mean body weights in the 300 mg/kg groups were 21% lower than those of the vehicle controls for males and 7% lower for females. Renal medullae were reddened in 5/5 male rats in the 600 mg/kg group, 1/5 female vehicle controls, 1/5 female rats in the 38 mg/kg group, and 1/5 female rats in the 600 mg/kg group.

The high dose selected for the 13-week studies was 300 mg/kg because the final mean body weight was lower than the initial mean weight in male rats receiving 600 mg/kg and there was no gain in mean body weight in female rats receiving 600 mg/kg.

THIRTEEN-WEEK STUDIES

Five of 10 male rats and 2/10 female rats that received 300 mg/kg died before the end of the studies (Table 10). Final mean body weights of male rats that received 150 or 300 mg/kg and of female rats that received 300 mg/kg were 30% or more lower than those of the vehicle controls; the final mean body weight of female rats receiving 150 mg/kg was 12% lower than that of the vehicle controls. No other compound-related clinical signs were reported.

Compound-related lesions were observed in the 300 mg/kg groups but not in the 150 mg/kg groups. In the 300 mg/kg group, compound-related effects were observed in the liver of 4/9 males and in the kidney of 4/9 males. The liver lesion consisted of centrilobular degeneration and was characterized by enlarged vacuolated cells and occasional necrotic cells with pyknotic nuclei and shrunken eosinophilic cytoplasm. In one male rat, excessive mitotic figures were

TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF BROMODICHLOROMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	123 ± 4	185 ± 7	+62 ± 4	--
38	5/5	122 ± 4	199 ± 5	+77 ± 4	108
75	5/5	123 ± 3	195 ± 3	+72 ± 3	105
150	5/5	121 ± 3	182 ± 7	+61 ± 5	98
300	5/5	122 ± 3	147 ± 5	+25 ± 3	79
600	5/5	121 ± 3	103 ± 4	−18 ± 3	56
FEMALE					
0	5/5	100 ± 2	130 ± 2	+30 ± 1	--
38	(d) 4/5	100 ± 2	134 ± 1	+35 ± 2	103
75	5/5	101 ± 2	136 ± 3	+35 ± 2	105
150	5/5	101 ± 2	134 ± 3	+33 ± 3	103
300	5/5	100 ± 2	121 ± 3	+21 ± 3	93
600	(e) 4/5	101 ± 2	101 ± 3	−1 ± 1	78

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Day of death: 8
(e) Day of death: 5

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BROMODICHLOROMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	145 ± 2	336 ± 5	+191 ± 4	--
19	10/10	145 ± 2	336 ± 4	+191 ± 4	100
38	10/10	146 ± 2	333 ± 5	+187 ± 4	99
75	10/10	145 ± 2	318 ± 2	+173 ± 3	95
150	10/10	145 ± 2	235 ± 4	+90 ± 4	70
300	(e) 5/10	146 ± 2	150 ± 6	0 ± 6	45
FEMALE					
0	10/10	111 ± 1	194 ± 2	+83 ± 2	--
19	10/10	112 ± 2	197 ± 2	+85 ± 2	102
38	10/10	112 ± 1	201 ± 2	+89 ± 3	104
75	10/10	111 ± 2	194 ± 3	+83 ± 2	100
150	10/10	111 ± 1	170 ± 4	+59 ± 3	88
300	(f) 8/10	114 ± 2	131 ± 4	+16 ± 5	68

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Final mean group body weight ± standard error of the mean
(d) Mean body weight change of the survivors of the group ± standard error of the mean
(e) Week of death: 8,12,12,12,12
(f) Week of death: 8,12

noted. Mild bile duct hyperplasia was also observed in these animals. The kidney changes in male rats at 300 mg/kg consisted of degeneration of proximal tubular epithelial cells, and 2/9 males had definite foci of coagulative necrosis of the tubular epithelium. Lymphoid atrophy of the thymus, spleen, and lymph nodes was observed in 4/9 high dose males. Mild to moderate atrophy of the seminal vesicles and/or prostate was present in 4/9 high dose males.

Compound-related changes were observed in the liver of 2/9 high dose (300 mg/kg) female rats and consisted of enlarged hepatocytes. Atrophy of the thymus, lymph nodes, and spleen occurred in high dose female rats but was much less than that observed in males. Rats in the high dose groups were emaciated and appeared to consume less feed on dosing days (although actual feed consumption was not measured).

Dose Selection Rationale: Based on deaths at 300 mg/kg, body weight gain depression at 150 and 300 mg/kg in male and female rats, lesions of the liver and kidney in male rats at 300 mg/kg, and lesions in the liver of female rats at 300 mg/kg, bromodichloromethane doses selected for rats for the 2-year studies were 50 and 100 mg/kg administered in corn oil by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial mean body weight of the high dose male rats was 6% lower than that of the vehicle controls (Table 11 and Figure 3). After week 16, the mean body weights of high dose male rats were 10%-17% lower than those of the vehicle controls, and those of high dose female rats were 5%-25% lower. After week 64, the mean body weights of high dose female rats were 17%-25% lower than those of the vehicle controls. Final mean body weights of low and high dose male rats were 106% and 88% that of vehicle controls, and final mean body weights of low and high dose female rats were 98% and 79% that of the vehicle controls. No compound-related clinical signs were observed.

TABLE 11. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

Weeks on Study	Vehicle Control		50 mg/kg			100 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	148	50	143	97	50	139	94	50
1	186	50	179	96	50	177	95	50
2	213	50	208	98	50	202	95	50
3	247	50	231	94	50	228	92	50
4	249	50	244	98	50	243	98	50
6	272	50	269	99	50	263	97	50
7	286	50	285	100	50	276	97	50
8	302	50	301	100	50	292	97	50
9	306	50	305	100	50	295	96	50
10	313	50	310	99	50	304	97	50
11	338	50	322	95	50	314	93	50
12	346	50	329	95	50	318	92	50
16	353	50	342	97	50	316	90	50
20	375	50	366	98	50	338	90	50
24	392	50	379	97	50	340	87	50
28	407	50	393	97	50	347	85	50
32	428	50	414	97	50	376	88	50
36	458	50	426	93	49	378	83	50
40	459	50	445	97	49	392	85	50
44	466	50	453	97	49	398	85	50
48	474	50	464	98	49	408	86	50
52	478	50	470	98	49	410	86	48
56	493	48	478	97	49	408	83	46
60	496	48	483	97	49	420	85	47
64	503	47	486	97	48	418	83	47
68	499	46	493	99	48	428	86	47
72	497	46	501	101	47	432	87	46
76	496	46	498	100	46	423	85	46
80	496	44	502	101	45	438	88	45
84	495	43	499	101	45	434	88	43
88	492	42	502	102	44	424	86	42
92	474	39	490	103	42	422	89	39
96	483	38	502	104	41	417	86	37
100	495	29	490	99	39	419	85	30
104	476	28	506	106	38	421	88	28
FEMALE								
0	103	50	104	101	50	104	101	50
1	124	50	121	98	50	121	98	50
2	137	50	132	96	50	135	99	50
3	148	50	143	97	50	141	95	50
4	160	50	154	96	50	153	96	50
5	169	50	161	95	50	161	95	50
6	174	50	169	97	50	171	98	50
7	181	50	174	96	50	175	97	50
8	186	50	179	96	50	180	97	50
9	193	50	185	96	50	188	97	50
10	199	50	189	95	50	191	96	50
11	203	50	197	97	50	196	97	50
12	205	50	202	99	50	196	96	50
16	215	50	206	96	50	205	95	50
20	224	50	216	96	50	209	93	50
24	229	50	222	97	50	216	94	50
28	238	50	233	98	50	225	95	50
32	242	50	238	98	50	219	90	50
36	251	50	245	98	49	231	92	49
40	260	50	250	96	49	233	90	49
44	261	49	255	98	49	236	90	49
48	269	49	263	98	49	239	89	49
52	271	49	264	97	49	238	88	48
56	282	49	268	95	48	245	87	48
60	287	49	276	96	48	245	85	48
64	292	49	281	96	48	238	82	48
68	301	49	291	97	48	249	83	48
72	312	49	296	95	45	246	79	48
76	321	48	302	94	44	247	77	47
80	322	48	308	96	43	254	79	47
84	335	45	320	96	39	256	76	47
88	334	45	323	97	38	257	77	46
92	345	45	324	94	37	260	75	45
96	341	41	332	97	35	263	77	44
100	344	38	334	97	32	263	76	42
104	340	34	332	98	27	269	79	41

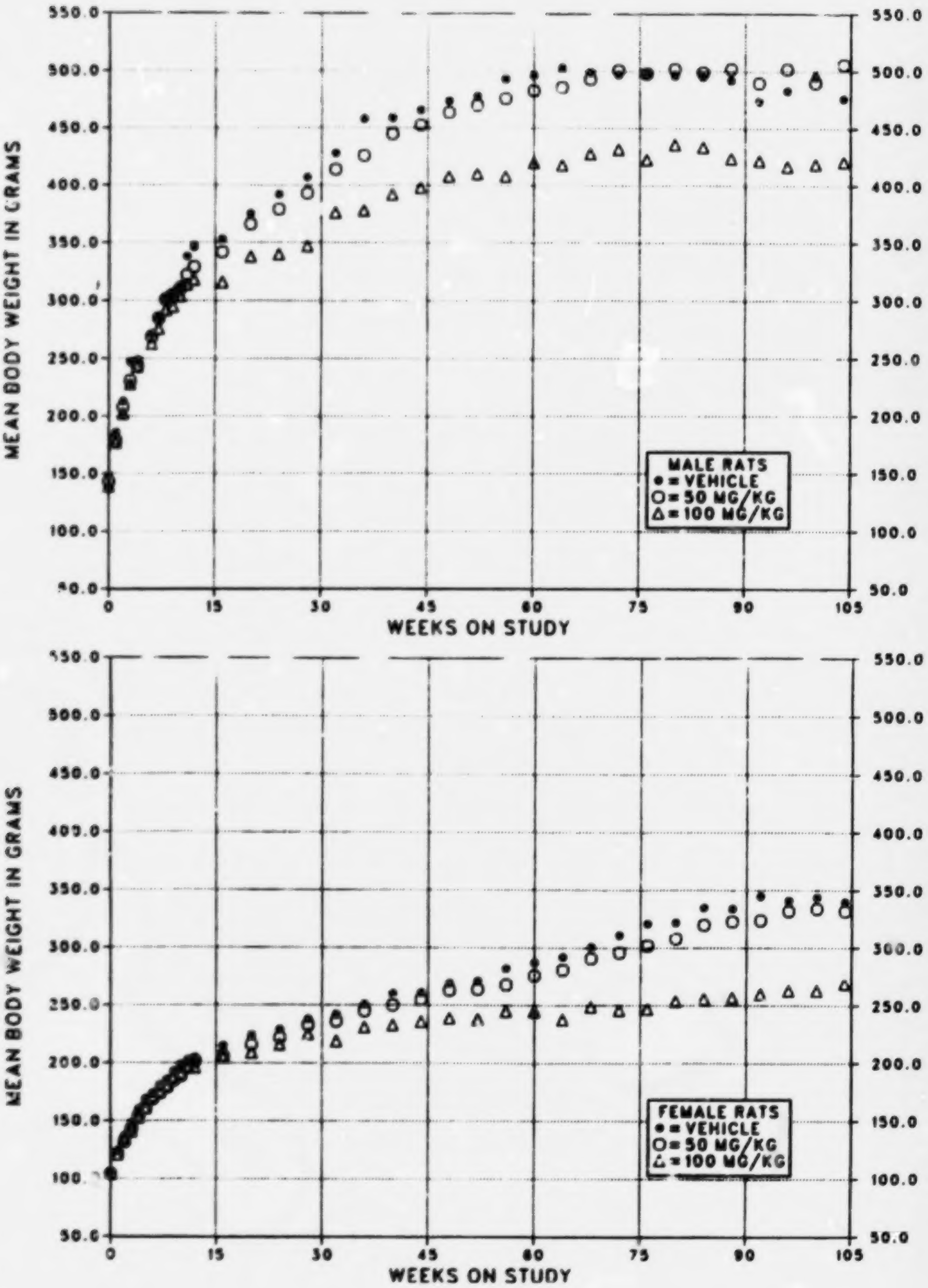

FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED BROMODICHLOROMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

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Survival

Estimates of the probabilities of survival for male and female rats administered bromodichloromethane at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 3. There were no significant differences in survival between dosed and vehicle control groups (Table 12).

TABLE 12. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	13	22
Accidentally killed	0	1	0
Killed at termination	27	36	28
Died during termination period	1	0	0
Survival P values (c)	1.000	0.105	0.998
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	23	9
Killed at termination	34	27	41
Survival P values (c)	0.206	0.168	0.187

(a) Terminal-kill period: weeks 104-105

(b) Includes animals killed in a moribund condition

(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

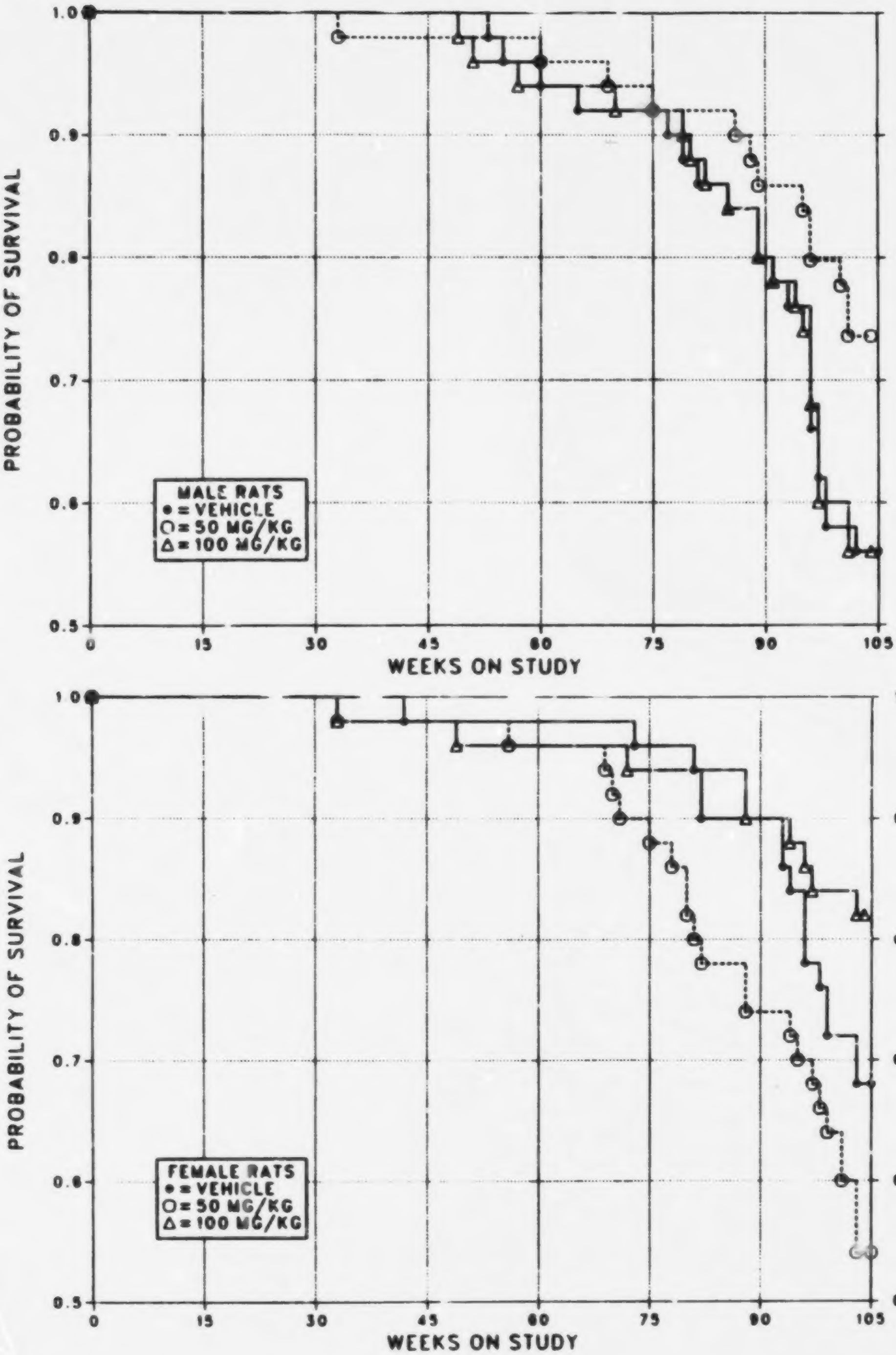

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED BROMODICHLOROMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

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Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the large intestine, kidney, skin, lung, liver, adrenal gland, anterior pituitary gland, and mammary gland.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in corn oil vehicle control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Historical incidences of tumors in corn oil vehicle control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

Large Intestine (Colon or Rectum): Adenomatous polyps and adenocarcinomas in male and female rats occurred with significant positive trends (Table 13). The incidences of adenomatous polyps and adenocarcinomas in high dose males and high dose females were significantly greater than those in the vehicle controls. The incidence of adenocarcinomas also was significantly elevated in low dose males. The adenomatous polyps and adenocarcinomas were generally pedunculated masses several millimeters to a centimeter in diameter, and they occurred in the colon and rectum. Adenomatous polyps consisted of a thickened, folded mucosal epithelium overlying a stalk of mature connective tissue. The epithelium was arranged in papillary (villous) or tubular patterns and did not show differentiation into goblet cells or normal absorptive cells. All the adenocarcinomas were minimally invasive and arose from adenomatous polyps. These lesions were diagnosed as adenocarcinomas when invasion or extension through the muscularis mucosa occurred and/or when the epithelium exhibited marked dysplasia and cellular atypia. Invasion of the submucosa by neoplastic cells was sometimes accompanied by a scirrhous response with marked proliferation of immature connective tissue.

Kidney: Cytomegaly of tubular epithelial cells was observed at increased incidences in dosed male rats (Table 14). Cytomegaly was not diagnosed in female rats. The incidence of nephrosis in high dose female rats was greater than that in the vehicle controls.

Tubular cell adenomas in female rats, tubular cell adenocarcinomas in male and female rats, and tubular cell adenomas or adenocarcinomas (combined) in male and female rats occurred with significant positive trends (Table 14). The incidences of tubular cell adenomas in high dose female rats and tubular cell adenocarcinomas and tubular cell adenomas or adenocarcinomas (combined) in high dose male and high dose female rats were significantly greater than those in the vehicle controls. Tubular cell hyperplasia was seen in three high dose male rats, two of which did not have kidney neoplasms. Tubular cell hyperplasia occurred in one low dose and four high dose female rats, none of which had kidney neoplasms.

TABLE 13. ANALYSIS OF TUMORS OF THE LARGE INTESTINE IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE (a)

	Vehicle Control	50 mg/kg	100 mg/kg
MALE			
Adenomatous Polyp			
Overall Rates	0/50 (0%)	3/50 (6%)	33/50 (66%)
Adjusted Rates	0.0%	7.6%	81.7%
Terminal Rates	0/28 (0%)	1/36 (3%)	21/28 (75%)
Week of First Observation		95	49
Life Table Tests	$P<0.001$	$P=0.163$	$P<0.001$
Incidental Tumor Tests	$P<0.001$	$P=0.067$	$P<0.001$
Adenocarcinoma			
Overall Rates	0/50 (0%)	11/50 (22%)	38/50 (76%)
Adjusted Rates	0.0%	28.5%	92.5%
Terminal Rates	0/28 (0%)	9/36 (25%)	25/28 (89%)
Week of First Observation		86	80
Life Table Tests	$P<0.001$	$P=0.002$	$P<0.001$
Incidental Tumor Tests	$P<0.001$	$P=0.001$	$P<0.001$
Adenomatous Polyp or Adenocarcinoma (b)			
Overall Rates	0/50 (0%)	13/50 (26%)	45/50 (90%)
Adjusted Rates	0.0%	32.0%	97.8%
Terminal Rates	0/28 (0%)	9/36 (25%)	27/28 (96%)
Week of First Observation		86	49
Life Table Tests	$P<0.001$	$P<0.001$	$P<0.001$
Incidental Tumor Tests	$P<0.001$	$P<0.001$	$P<0.001$
FEMALE			
Adenomatous Polyp			
Overall Rates	0/46 (0%)	0/50 (0%)	7/47 (15%)
Adjusted Rates	0.0%	0.0%	16.8%
Terminal Rates	0/32 (0%)	0/27 (0%)	6/40 (15%)
Week of First Observation			88
Life Table Tests	$P=0.003$	(c)	$P=0.018$
Incidental Tumor Tests	$P=0.002$	(c)	$P=0.010$
Adenocarcinoma			
Overall Rates	0/46 (0%)	0/50 (0%)	6/47 (13%)
Adjusted Rates	0.0%	0.0%	15.0%
Terminal Rates	0/32 (0%)	0/27 (0%)	6/40 (15%)
Week of First Observation			104
Life Table Tests	$P=0.007$	(c)	$P=0.032$
Incidental Tumor Tests	$P=0.007$	(c)	$P=0.032$
Adenomatous Polyp or Adenocarcinoma (d)			
Overall Rates	0/46 (0%)	0/50 (0%)	12/47 (26%)
Adjusted Rates	0.0%	0.0%	29.1%
Terminal Rates	0/32 (0%)	0/27 (0%)	11/40 (28%)
Week of First Observation			88
Life Table Tests	$P<0.001$	(c)	$P=0.001$
Incidental Tumor Tests	$P<0.001$	(c)	$P<0.001$

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence at study laboratory (mean): 0/250; historical incidence in NTP studies: 3/1,390 (0.2%)
(c) No P value is reported because no tumors were observed in the 50 mg/kg and vehicle control groups.
(d) Historical incidence at study laboratory: 0/236; historical incidence in NTP studies: 0/1,400

TABLE 14. ANALYSIS OF KIDNEY LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
MALE			
Cytomegaly of Tubular Epithelial Cells			
Overall Rates	0/50 (0%)	18/50 (36%)	44/50 (88%)
Tubular Cell Hyperplasia			
Overall Rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Tubular Cell Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates	0.0%	2.8%	9.3%
Terminal Rates	0/28 (0%)	1/36 (3%)	1/28 (4%)
Week of First Observation		104	96
Life Table Tests	P=0.056	P=0.550	P=0.125
Incidental Tumor Tests	P=0.065	P=0.550	P=0.120
Tubular Cell Adenocarcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	10/50 (20%)
Adjusted Rates	0.0%	0.0%	32.3%
Terminal Rates	0/28 (0%)	0/36 (0%)	8/28 (29%)
Week of First Observation			89
Life Table Tests	P<0.001	(a)	P=0.001
Incidental Tumor Tests	P<0.001	(a)	P=0.001
Tubular Cell Adenoma or Adenocarcinoma (b)			
Overall Rates	0/50 (0%)	1/50 (2%)	13/50 (26%)
Adjusted Rates	0.0%	2.8%	39.5%
Terminal Rates	0/28 (0%)	1/36 (3%)	9/28 (32%)
Week of First Observation		104	89
Life Table Tests	P<0.001	P=0.550	P<0.001
Incidental Tumor Tests	P<0.001	P=0.550	P<0.001
FEMALE			
Nephrosis			
Overall Rates	26/50 (52%)	17/50 (34%)	41/50 (82%)
Tubular Cell Hyperplasia			
Overall Rates	0/50 (0%)	1/50 (2%)	4/50 (8%)
Tubular Cell Adenoma			
Overall Rates	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rates	0.0%	3.7%	14.6%
Terminal Rates	0/34 (0%)	1/27 (4%)	6/41 (15%)
Week of First Observation		105	104
Life Table Tests	P=0.011	P=0.454	P=0.030
Incidental Tumor Tests	P=0.011	P=0.454	P=0.030
Tubular Cell Adenocarcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	9/50 (18%)
Adjusted Rates	0.0%	0.0%	21.4%
Terminal Rates	0/34 (0%)	0/27 (0%)	8/41 (20%)
Week of First Observation			103
Life Table Tests	P<0.001	(a)	P=0.006
Incidental Tumor Tests	P<0.001	(a)	P=0.003
Tubular Cell Adenoma or Adenocarcinoma (c)			
Overall Rates	0/50 (0%)	1/50 (2%)	15/50 (30%)
Adjusted Rates	0.0%	3.7%	35.7%
Terminal Rates	0/34 (0%)	1/27 (4%)	14/41 (34%)
Week of First Observation		105	103
Life Table Tests	P<0.001	P=0.454	P<0.001
Incidental Tumor Tests	P<0.001	P=0.454	P<0.001

(a) No P value is reported because no tumors were observed in the 50 mg/kg and vehicle control groups.
(b) Historical incidence at study laboratory (mean): 1/250 (0.4%); historical incidence in NTP studies: 8/1,448 (0.6 %)
(c) Historical incidence at study laboratory (mean): 0/250; historical incidence in NTP studies: 2/1,447 (0.1%)

Skin: The incidence of squamous cell papillomas or carcinomas (combined) in low dose but not in high dose male rats was significantly greater than that in the vehicle controls (Table 15).

Lung: Alveolar/bronchiolar adenomas or carcinomas (combined) in male rats occurred with a significant positive trend, but the incidences in the dosed groups were not significantly greater than that in the concurrent vehicle controls; the incidence in the high dose group was equal to the highest recorded in vehicle controls at this laboratory (Table 16; Table A4d). The incidences in the dosed female groups were identical to that in the vehicle control group (vehicle control, 1/50; low dose, 1/50; high dose, 1/50).

Liver: Necrosis was observed at slightly increased incidences in dosed male rats (Table 17). Clear cell change, eosinophilic cytoplasmic change, and focal cellular change were observed at increased incidences in high dose female rats. Fatty metamorphosis was observed at increased incidences in dosed male and female rats.

TABLE 15. ANALYSIS OF SKIN TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	3/50 (6%)	0/50 (0%)
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	3/50 (6%)	0/50 (0%)
Squamous Cell Papilloma or Carcinoma (a)			
Overall Rates	0/50 (0%)	6/50 (12%)	0/50 (0%)
Adjusted Rates	0.0%	16.7%	0.0%
Terminal Rates	0/28 (0%)	6/36 (17%)	0/28 (0%)
Week of First Observation		104	
Life Table Tests	P=0.606	P=0.034	(b)
Incidental Tumor Tests	P=0.606	P=0.034	(b)

(a) Historical incidence at study laboratory (mean ± SD): 7/250 (3% ± 4%); historical incidence in NTP studies: 38/1,450 (3% ± 3%)

(b) No P value is reported because no tumors were observed in the 100 mg/kg and vehicle control groups.

TABLE 16. ANALYSIS OF LUNG TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
Alveolar/Bronchiolar Adenoma			
Overall Rates	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates	0.0%	5.6%	9.7%
Terminal Rates	0/28 (0%)	2/36 (6%)	2/28 (7%)
Week of First Observation		104	96
Life Table Tests	P=0.073	P=0.295	P=0.120
Incidental Tumor Tests	P=0.079	P=0.295	P=0.123
Alveolar/Bronchiolar Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Alveolar/Bronchiolar Adenoma or Carcinoma (a)			
Overall Rates	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted Rates	0.0%	5.6%	13.1%
Terminal Rates	0/28 (0%)	2/36 (6%)	3/28 (11%)
Week of First Observation		104	96
Life Table Tests	P=0.031	P=0.295	P=0.062
Incidental Tumor Tests	P=0.034	P=0.295	P=0.064

(a) Historical incidence at study laboratory (mean ± SD): 12/249 (5% ± 2%); historical incidence in NTP studies: 47/1,448 (3% ± 3%)

TABLE 17. NUMBER OF RATS WITH LIVER LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

Lesion	Vehicle Control	50 mg/kg	100 mg/kg
MALE			
No. of livers examined	50	50	50
Clear cell change	23	21	24
Eosinophilic cytoplasmic change	0	1	2
Focal cellular change	0	0	1
Fatty metamorphosis	36	48	47
Necrosis	1	4	6
Neoplastic nodule	1	0	3
Hepatocellular carcinoma	0	0	1
FEMALE			
No. of livers examined	50	50	50
Clear cell change	4	6	39
Eosinophilic cytoplasmic change	0	1	11
Focal cellular change	4	4	11
Fatty metamorphosis	7	22	13
Necrosis	1	3	1
Neoplastic nodule	1	3	1
Hepatocellular carcinoma	0	0	0

Adrenal Gland: Pheochromocytomas in male rats occurred with a significant negative trend. The incidence in the high dose group was significantly lower than that in the vehicle controls (Table 18).

Anterior Pituitary Gland: Adenomas and adenomas or carcinomas (combined) in female rats occurred with significant negative trends, and the incidences in the dosed groups were significantly lower than those in the vehicle controls (Table 19).

Mammary Gland: Fibroadenomas in female rats occurred with a significant negative trend; the incidence in high dose female rats was significantly lower than that in the vehicle controls (Table 20).

TABLE 18. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
Medullary Hyperplasia			
Overall Rates	9/50 (18%)	7/50 (14%)	10/50 (20%)
Pheochromocytoma			
Overall Rates	17/50 (34%)	13/50 (26%)	3/50 (6%)
Adjusted Rates	50.0%	34.0%	8.6%
Terminal Rates	12/28 (43%)	11/36 (31%)	1/28 (4%)
Week of First Observation	79	96	89
Life Table Tests	P<0.001N	P=0.089N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.200N	P<0.001N
Malignant Pheochromocytoma			
Overall Rates	1/50 (2%)	2/50 (4%)	2/50 (4%)
Pheochromocytoma or Malignant Pheochromocytoma (a)			
Overall Rates	18/50 (36%)	14/50 (28%)	5/50 (10%)
Adjusted Rates	53.1%	35.6%	13.9%
Terminal Rates	13/28 (46%)	11/36 (31%)	2/28 (7%)
Week of First Observation	79	89	70
Life Table Tests	P=0.002N	P=0.091N	P=0.003N
Incidental Tumor Tests	P=0.002N	P=0.217N	P=0.003N

(a) Historical incidence at study laboratory (mean ± SD): 57/250 (23% ± 5%); historical incidence in NTP studies: 347/1,442 (24% ± 9%)

TABLE 19. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
Focal Hyperplasia			
Overall Rates	3/49 (6%)	11/49 (22%)	8/49 (16%)
Adenoma			
Overall Rates	27/49 (55%)	18/49 (37%)	13/49 (27%)
Adjusted Rates	67.1%	47.3%	30.7%
Terminal Rates	21/34 (62%)	9/27 (33%)	12/41 (29%)
Week of First Observation	81	70	72
Life Table Tests	P=0.001N	P=0.259N	P<0.001N
Incidental Tumor Tests	P=0.002N	P=0.044N	P=0.002N
Carcinoma			
Overall Rates	4/49 (8%)	2/49 (4%)	1/49 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	31/49 (63%)	20/49 (41%)	14/49 (29%)
Adjusted Rates	75.3%	50.2%	33.1%
Terminal Rates	24/34 (71%)	9/27 (33%)	13/41 (32%)
Week of First Observation	81	70	72
Life Table Tests	P<0.001N	P=0.194N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.021N	P<0.001N

(a) Historical incidence at study laboratory (mean ± SD): 95/245 (39% ± 6%); historical incidence in NTP studies: 561/1,407 (40% ± 8%)

TABLE 20. ANALYSIS OF MAMMARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
Hyperplasia			
Overall Rates	18/50 (36%)	13/50 (26%)	2/50 (4%)
Fibroadenoma (a)			
Overall Rates	20/50 (40%)	15/50 (30%)	1/50 (2%)
Adjusted Rates	49.3%	45.5%	2.4%
Terminal Rates	14/34 (41%)	10/27 (37%)	1/41 (2%)
Week of First Observation	82	80	104
Life Table Tests	P<0.001N	P=0.472N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.345N	P<0.001N

(a) Historical incidence at study laboratory (mean ± SD): 84/250 (34% ± 3%); historical incidence in NTP studies: 365/1,450 (25% ± 8%).

III. RESULTS: MICE

SINGLE-ADMINISTRATION STUDIES

All mice that received 1,250 or 2,500 mg/kg bromodichloromethane and 5/5 male mice and 2/5 female mice that received 600 mg/kg died before the end of the studies (Table 21). Male mice that received 600 or 1,250 mg/kg and female mice that received 600, 1,250, or 2,500 mg/kg were lethargic. The liver was pale and the cranial cavity contained blood in animals in the 1,250 or 2,500 mg/kg groups. No dose-related body weight effects were seen in animals that survived to the end of the 14-day observation period. The high dose selected for the 14-day studies was 300 mg/kg because deaths occurred at 600 mg/kg and above in the single-administration studies.

FOURTEEN-DAY STUDIES

All male mice that received 150 or 300 mg/kg bromodichloromethane and 1/5 female mice that received 300 mg/kg died before the end of the studies (Table 22). The death of the female mouse was a result of an accident. All male mice that received 150 or 300 mg/kg were lethargic and dehydrated and had hunched posture. The final mean body weights of the surviving mice were comparable. The renal medullae were reddened in 4/5 males that received 150 mg/kg, 5/5 males that received 300 mg/kg, and 1/5 females that received 150 mg/kg. The high dose selected for the 13-week study in male mice was 100 mg/kg because all male mice in the 14-day study died at 150 mg/kg and above. The high dose selected for the 13-week study in female mice was 400 mg/kg because no body weight effect or compound-related mortality was seen at 300 mg/kg in the 14-day study.

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF BROMODICHLOROMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE (d)				
150	5/5	23.5 ± 0.8	26.2 ± 0.9	+2.7 ± 0.7
300	5/5	23.2 ± 0.7	25.2 ± 0.9	+2.0 ± 0.3
600	0/5	23.2 ± 0.6	(e)	(e)
1,250	0/5	23.2 ± 0.8	(e)	(e)
2,500	0/5	22.9 ± 0.5	(e)	(e)
FEMALE (f)				
150	5/5	16.5 ± 0.7	20.4 ± 0.2	+3.9 ± 0.7
300	5/5	16.4 ± 0.6	20.6 ± 0.4	+4.2 ± 0.7
600	3/5	16.3 ± 0.7	20.0 ± 1.0	+3.8 ± 2.2
1,250	0/5	16.2 ± 0.9	(e)	(e)
2,500	0/5	16.5 ± 0.9	(e)	(e)

(a) Number surviving/number initially in the group; all deaths occurred within 3 days of dosing.

(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.

(c) Mean body weight change of the survivors of the group ± standard error of the mean

(d) The survival pattern precludes meaningful LD_{50} calculations.

(e) No data are reported due to the 100% mortality in this group.

(f) LD_{50} value by the Spearman-Karber method: 651 mg/kg with a 95% confidence interval of 462-917 mg/kg

TABLE 22. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF BROMODICHLOROMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
MALE					
0	5/5	23.1 ± 0.8	25.2 ± 0.7	+2.1 ± 0.3	--
19	5/5	22.9 ± 0.7	25.0 ± 0.8	+2.1 ± 0.4	99.2
38	5/5	23.2 ± 0.7	25.2 ± 1.0	+2.0 ± 0.5	100.0
75	5/5	22.9 ± 0.5	25.4 ± 0.6	+2.5 ± 0.3	100.8
150	(d) 0/5	23.1 ± 0.6	(e)	(e)	(e)
300	(f) 0/5	23.6 ± 0.8	(e)	(e)	(e)
FEMALE					
0	5/5	18.7 ± 0.5	20.0 ± 0.4	+1.3 ± 0.6	--
19	5/5	18.6 ± 0.4	20.4 ± 0.2	+1.8 ± 0.5	102.0
38	5/5	18.5 ± 0.3	21.0 ± 0.3	+2.5 ± 0.5	105.0
75	5/5	18.5 ± 0.4	19.8 ± 0.2	+1.3 ± 0.2	99.0
150	5/5	18.7 ± 0.2	20.4 ± 0.4	+1.7 ± 0.3	102.0
300	(g) 4/5	18.7 ± 0.3	19.8 ± 0.3	+0.9 ± 0.3	99.0

(a) Number surviving/number initially in the group

(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.

(c) Mean body weight change of the survivors of the group ± standard error of the mean

(d) Day of death: 4,4,5,8,8

(e) No data are reported due to the 100% mortality in this group.

(f) Day of death: 3,3,4,4,4

(g) Death judged to be accidental

THIRTEEN-WEEK STUDIES

All mice survived to the end of the studies (Table 23). The final mean body weight of males that received 100 mg/kg was 9% lower than that of the vehicle controls. The final mean body weight of females that received 200 or 400 mg/kg was 94%-95% that of the vehicle controls. Focal necrosis of the proximal renal tubular epithelium occurred in 6/10 males that received 100 mg/kg. Nephrosis of minimal severity occurred in 2/10 males that received 100 mg/kg. No compound-related lesions were seen in the 50 mg/kg groups. Hepatocytes in the centrilobular area of the liver of 8/10 female mice at 400 mg/kg and 7/10 female mice at 200 mg/kg were enlarged with vacuolated or foamy cytoplasm characteristic of lipid accumulation. Microgranulomas were present in the liver of 7/10 female mice that received 200 mg/kg. No compound-related lesions were noted in the 100 mg/kg female group. No compound-related clinical signs were noted.

Dose Selection Rationale: Based on weight gain depression and liver and kidney lesions observed at 100 mg/kg, bromodichloromethane doses selected for male mice for the 2-year study were 25 and 50 mg/kg administered in corn oil by gavage. Based on liver lesions and body weight gain depression seen at 200 and 400 mg/kg, but not at 100 mg/kg, doses selected for female mice for the 2-year study were 75 and 150 mg/kg.

TABLE 23. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF BROMODICHLOROMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final (c)	Change (d)	
MALE					
0	10/10	26.9 ± 0.6	35.2 ± 0.7	+8.3 ± 0.9	--
6.25	10/10	27.4 ± 0.8	37.0 ± 1.1	+9.6 ± 0.6	105.1
12.5	10/10	27.2 ± 0.4	35.5 ± 0.8	+8.3 ± 0.9	100.9
25	10/10	26.8 ± 0.6	34.7 ± 0.8	+7.9 ± 0.6	98.6
50	10/10	27.1 ± 0.6	35.2 ±0.9	+8.1 ± 0.5	100.0
100	10/10	27.0 ± 0.6	32.2 ± 0.6	+5.2 ± 0.5	91.5
FEMALE					
0	10/10	20.4 ± 0.4	26.2 ± 0.4	+5.8 ± 0.4	--
25	10/10	20.8 ± 0.5	27.7 ± 1.3	+6.9 ± 0.9	105.7
50	10/10	21.0 ± 0.5	28.1 ± 1.0	+7.1 ± 0.7	107.3
100	10/10	20.4 ± 0.4	26.6 ± 0.6	+6.2 ± 0.5	101.5
200	10/10	20.3 ± 0.4	25.0 ± 0.4	+4.7 ± 0.1	95.4
400	10/10	20.6 ± 0.4	24.6 ± 0.4	+4.0 ± 0.1	93.9

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean
(c) Final mean group body weight ± standard error of the mean
(d) Mean body weight change of the group ± standard error of the mean

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Throughout the studies, the mean body weights of the high dose male mice were never more than 10% lower than those of the vehicle controls (Table 24 and Figure 5). Mean body weights of low dose and vehicle control male mice were comparable. Final mean body weights of low and high dose male mice were 99% and 95% that of the vehicle controls. Mean body weights of high dose female mice relative to those of the vehicle controls decreased progressively throughout the study, reaching a low of 64% of the vehicle controls' weight at weeks 92 and 96. Final mean body weights of low and high dose female mice were 91% and 75% that of the vehicle controls. No compound-related clinical signs were observed.

TABLE 24. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. cortrols)	No. of Survivors
MALE				**25 mg/kg**			**50 mg/kg**	
0	24.5	50	24.8	101	50	24.5	100	50
1	26.2	48	26.5	101	49	25.9	99	50
2	27.4	48	28.0	102	49	26.4	96	50
3	28.4	48	28.8	101	49	27.3	96	50
4	29.6	48	29.8	101	49	28.5	96	50
5	30.4	48	30.7	101	49	28.5	94	50
6	31.6	48	31.7	100	49	29.9	95	50
7	32.3	48	32.5	101	49	30.6	95	50
8	33.3	48	33.2	100	49	31.3	94	50
9	33.8	47	34.1	101	49	31.6	93	50
10	34.7	47	34.8	100	49	32.4	93	50
11	34.8	47	35.3	101	49	32.8	94	50
12	34.7	47	34.8	100	49	32.8	95	50
16	37.7	47	34.7	92	49	35.5	94	48
20	39.0	47	38.2	98	49	37.1	95	47
24	40.1	47	40.5	101	49	38.5	96	47
28	40.3	47	40.6	101	49	36.5	91	46
32	42.6	47	42.5	100	49	40.0	94	46
36	43.7	47	43.8	100	49	41.1	94	46
40	43.9	47	44.3	101	49	41.6	95	46
44	44.5	47	44.4	100	49	41.0	92	46
48	44.6	47	44.7	100	49	41.4	93	46
52	43.0	47	43.7	102	49	40.8	95	46
56	43.5	47	44.1	101	49	42.7	98	46
60	44.3	47	44.2	100	49	41.8	94	46
64	44.5	47	43.1	97	48	42.7	96	46
68	43.1	47	42.8	99	48	40.9	95	46
72	42.5	47	43.8	103	43	41.4	97	46
76	42.7	47	42.5	100	42	39.9	93	46
80	42.9	45	42.4	99	42	41.2	96	45
84	43.2	42	42.9	99	40	41.6	96	45
88	43.0	41	42.8	99	39	41.0	95	45
92	43.2	39	42.7	99	37	41.1	95	44
96	42.6	37	42.4	100	36	40.4	95	43
100	42.3	36	41.8	99	34	40.3	95	42
104	41.2	34	40.7	99	32	39.1	95	42
FEMALE				**75 mg/kg**			**150 mg/kg**	
0	18.5	50	20.6	111	50	20.8	112	50
1	21.3	48	21.4	100	50	20.9	98	50
2	22.5	47	22.1	98	50	22.5	100	50
3	22.7	47	22.1	97	50	22.1	97	50
4	24.1	47	23.0	95	50	23.3	97	50
5	24.5	47	23.6	96	50	23.6	96	50
6	24.9	47	24.1	97	50	24.0	96	50
7	25.5	47	24.5	96	50	24.3	95	50
8	25.7	47	24.9	97	50	24.6	96	50
9	26.4	47	25.5	97	50	25.4	96	50
10	26.4	46	26.2	99	50	26.1	99	50
11	26.4	46	25.6	97	50	25.2	95	50
12	27.1	46	26.3	97	50	25.8	95	50
16	30.9	46	28.6	93	50	28.3	92	50
20	33.0	46	30.4	92	50	29.8	90	50
24	35.2	46	32.4	92	50	29.7	84	50
28	34.5	46	33.1	96	50	29.8	86	50
32	37.3	46	34.8	93	50	31.0	83	50
36	39.5	46	36.8	93	50	32.4	82	50
40	41.2	46	38.3	93	50	33.0	80	50
44	43.3	46	38.9	90	50	34.6	80	47
48	43.6	46	38.8	89	50	32.5	75	46
52	44.4	46	39.2	88	48	32.6	73	45
56	44.0	46	39.0	89	48	33.0	75	43
60	45.9	45	39.0	85	46	32.7	71	39
64	45.0	45	38.2	85	41	32.0	71	35
68	44.8	45	38.0	85	39	30.8	69	33
72	44.9	43	39.8	89	38	33.0	73	33
76	44.5	42	39.4	89	35	32.1	72	31
80	45.1	41	38.9	86	32	31.5	70	28
84	44.3	41	38.9	88	26	29.6	67	27
88	46.3	37	41.5	90	23	31.2	67	25
92	48.0	32	40.8	85	21	30.6	64	24
96	47.1	30	40.1	85	19	30.0	64	21
100	46.2	29	39.4	85	15	31.1	67	18
104	41.3	26	37.6	91	14	31.1	75	15

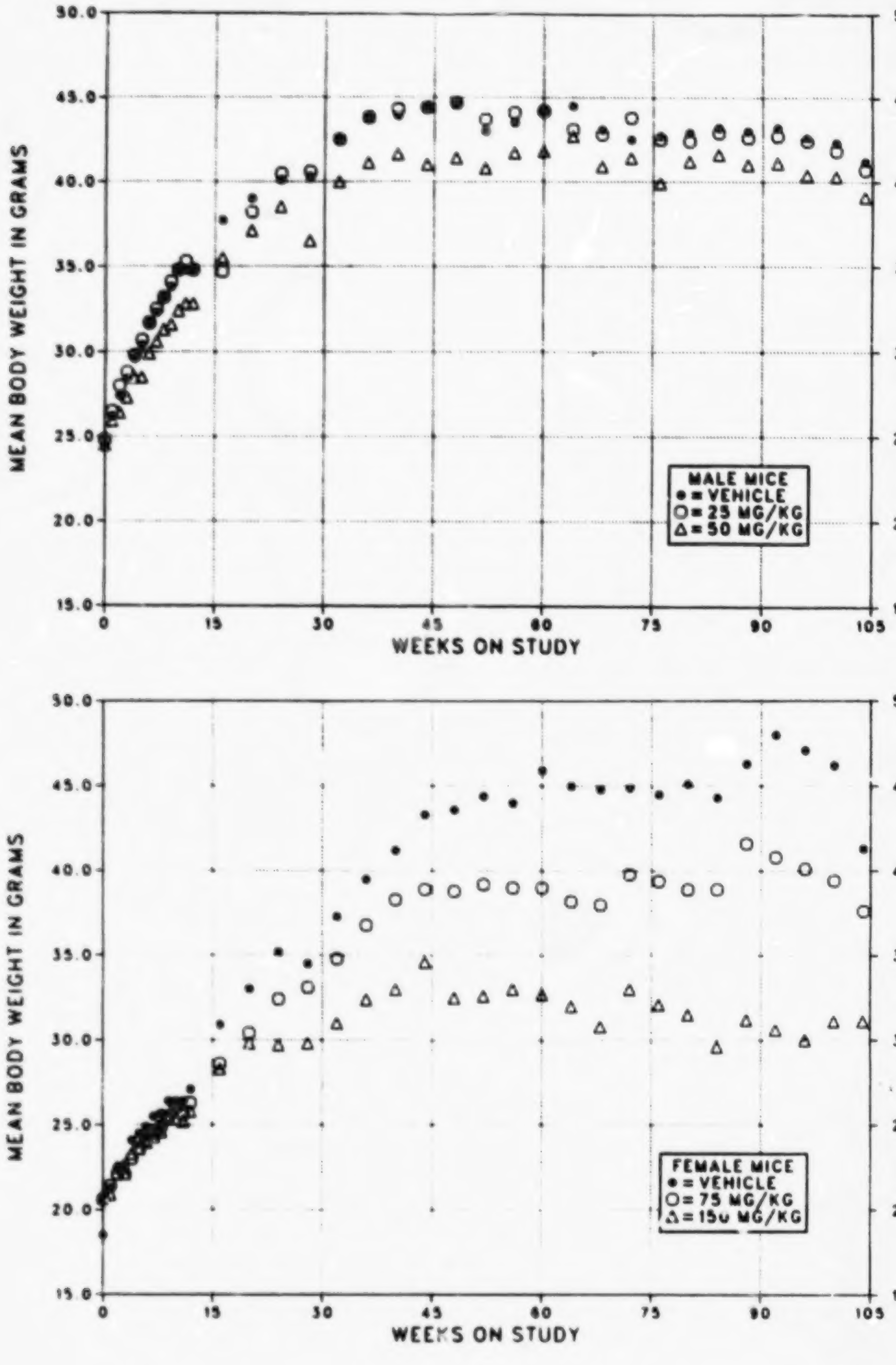

FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED BROMODICHLOROMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

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Survival

Estimates of the probabilities of survival for male and female mice administered bromodichloromethane at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 6. Survival of dosed male mice was comparable to that of the vehicle controls (Table 25). The survival of both the low dose group (after week 79) and high dose group (after week 61) of female mice was significantly lower than that of the vehicle controls, and this decreased survival was associated in part with ovarian abscesses (vehicle control, 8/50, 16%; low dose, 19/47, 40%; high dose, 18/49, 38%).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the kidney, liver, anterior pituitary gland, thyroid gland, ovary, and testis.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Historical incidences of tumors in corn oil vehicle control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Historical incidences of tumors in corn oil vehicle control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

TABLE 25. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

	Vehicle Control	Low Dose	High Dose
MALE (a)		**25 mg/kg**	**50 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	18	8
Accidentally killed	2	0	0
Animals missing	1	0	0
Killed at termination	34	31	42
Died during termination period	0	1	0
Survival P values (c)	0.288	0.408	0.288
FEMALE (a)		**75 mg/kg**	**150 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	37	35
Accidentally killed	2	0	0
Killed at termination	26	13	15
Survival P values (c)	0.006	0.003	0.009

(a) Terminal-kill period: male--weeks 104-105; female--week 105

(b) Includes animals killed in a moribund condition

(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

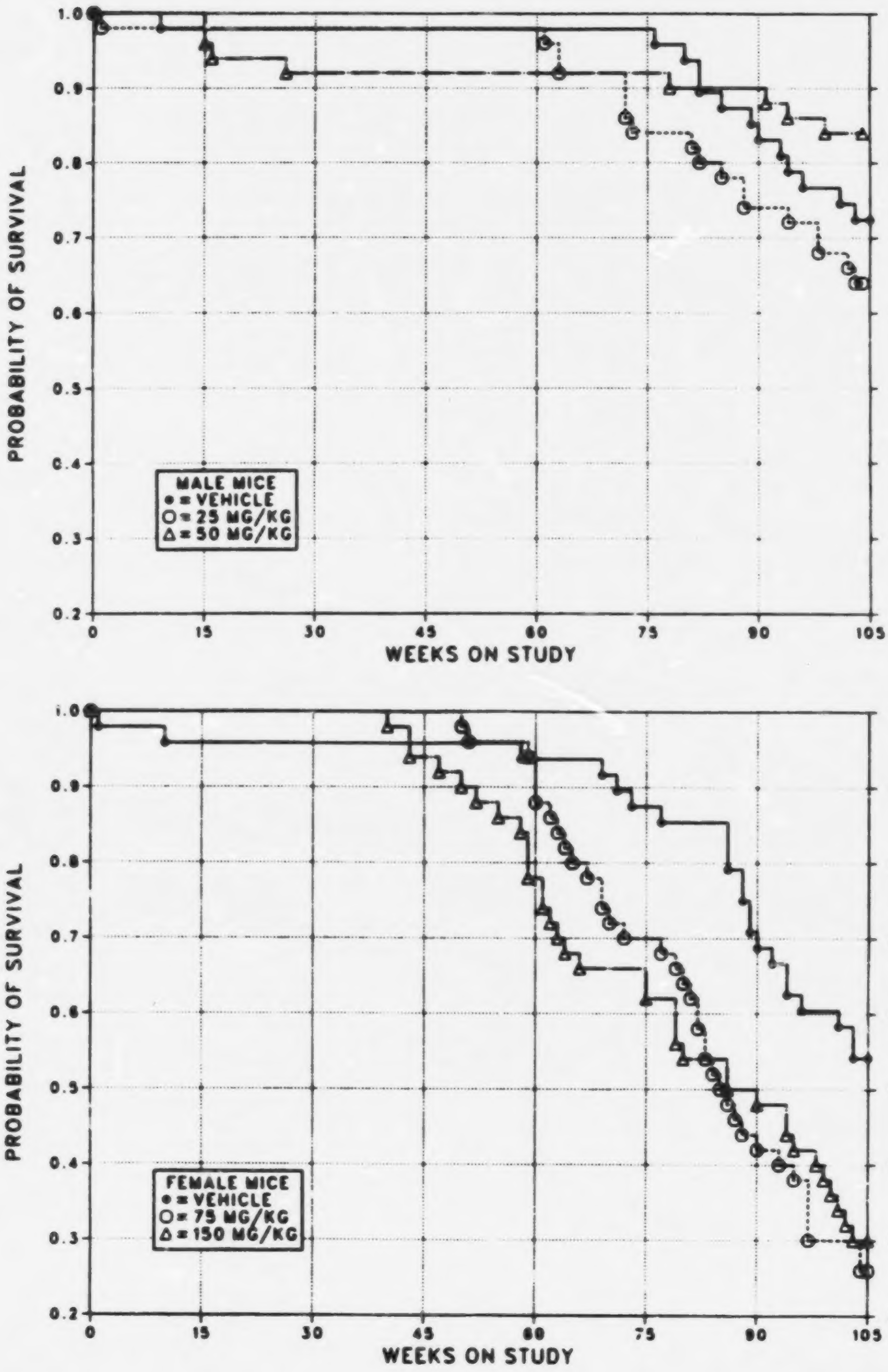

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED BROMODICHLOROMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Kidney: Most dosed male mice had renal cytomegaly consisting of enlargement of both the cytoplasm and nucleus of isolated renal tubular cells (vehicle control, 0/49; low dose, 41/50; high dose, 47/50). The nuclei of affected cells tended to show chromatin clumping and a prominent nuclear membrane. This change was not seen in females. Renal tubular cell adenomas or adenocarcinomas (combined) in male mice occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 26). Renal tubular cell neoplasms were not diagnosed in female mice. The adenomas were small, discrete aggregations of basophilic cells arranged in small nests or larger clusters. Tubular cell adenocarcinomas were larger than adenomas and showed increased cellular atypia and occasionally necrosis and/or invasion of the renal capsule.

TABLE 26. ANALYSIS OF KIDNEY TUBULAR CELL TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Adenoma			
Overall Rates	1/49 (2%)	2/50 (4%)	6/50 (12%)
Adjusted Rates	2.9%	6.3%	14.3%
Terminal Rates	1/34 (3%)	2/32 (6%)	6/42 (14%)
Week of First Observation	104	104	104
Life Table Tests	P=0.056	P=0.479	P=0.098
Incidental Tumor Tests	P=0.056	P=0.479	P=0.098
Adenocarcinoma			
Overall Rates	0/49 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	9.5%
Terminal Rates	0/34 (0%)	0/32 (0%)	4/42 (10%)
Week of First Observation			104
Life Table Tests	P=0.026	(b)	P=0.093
Incidental Tumor Tests	P=0.026	(b)	P=0.093
Adenoma or Adenocarcinoma (c)			
Overall Rates	1/49 (2%)	2/50 (4%)	9/50 (18%)
Adjusted Rates	2.9%	6.3%	21.4%
Terminal Rates	1/34 (3%)	2/32 (6%)	9/42 (21%)
Week of First Observation	104	104	104
Life Table Tests	P=0.008	P=0.479	P=0.022
Incidental Tumor Tests	P=0.008	P=0.479	P=0.022

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C, Table C3 (footnotes).
(b) No P value is reported because no tumors were observed in the 25 mg/kg and vehicle control groups.
(c) Historical incidence at study laboratory (mean): 2/299 (0.7%); historical incidence in NTP studies: 5/1,490 (0.3%)

Liver: The incidence of fatty metamorphosis was notably increased in dosed male mice (male: vehicle control, 4/49; low dose, 8/50; high dose, 19/50; female: 11/50; 16/48; 15/50).

Hepatocellular adenomas and carcinomas occurred with significant positive trends in female mice, and the incidences in the high dose group were significantly greater than those in the vehicle controls (Table 27). The incidences of adenomas and adenomas or carcinomas (combined) in the low dose group were significantly greater than those in the vehicle controls. The incidences of hepatocellular adenomas or carcinomas (combined) in dosed and vehicle control male mice were comparable (vehicle control, 17/49; low dose, 16/50; high dose, 20/50).

TABLE 27. ANALYSIS OF HEPATOCELLULAR LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	75 mg/kg	150 mg/kg
Hyperplasia			
Overall Rates	0/50 (0%)	1/48 (2%)	3/50 (6%)
Adenoma			
Overall Rates	1/50 (2%)	13/48 (27%)	23/50 (46%)
Adjusted Rates	3.4%	75.2%	91.3%
Terminal Rates	0/26 (0%)	9/13 (69%)	13/15 (87%)
Week of First Observation	101	88	62
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Carcinoma			
Overall Rates	2/50 (4%)	5/48 (10%)	10/50 (20%)
Adjusted Rates	7.7%	23.3%	45.7%
Terminal Rates	2/26 (8%)	1/13 (8%)	4/15 (27%)
Week of First Observation	105	83	86
Life Table Tests	P=0.001	P=0.065	P=0.001
Incidental Tumor Tests	P=0.003	P=0.172	P=0.006
Adenoma or Carcinoma (a)			
Overall Rates	3/50 (6%)	18/48 (38%)	29/50 (58%)
Adjusted Rates	10.9%	84.7%	100.0%
Terminal Rates	2/26 (8%)	10/13 (77%)	15/15 (100%)
Week of First Observation	101	83	62
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001

(a) Historical incidence at study laboratory (mean ± SD): 30/298 (10% ± 5%); historical incidence in NTP studies: 116/1,489 (8% ± 6%).

Anterior Pituitary Gland: Adenomas in female mice occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the vehicle controls (Table 28).

Thyroid Gland: The incidences of follicular cell hyperplasia were increased in dosed male and female mice (male: vehicle control, 0/48; low dose, 3/44; high dose, 5/49; female: 6/50; 18/45; 21/48). The incidence of follicular cell adenomas was not increased in dosed mice (male: 2/48; 0/44; 0/49; female: 1/50; 2/45; 1/48).

Ovary: Ovarian abscesses were found in all dosed female groups, and the incidences in the dosed groups were greater than that in the vehicle controls (vehicle control, 8/50; low dose, 19/47; high dose, 18/49). All diagnoses of this lesion were in animals that died before the end of the study. The lesions were large (1-2 cm), thin-walled cysts involving the proximal fallopian tube and ovaries which were filled with polymorphonuclear leukocytes and necrotic debris. The abscesses sometimes ruptured, producing acute peritonitis. They were frequently bilateral and were a leading cause of early death among female mice.

Testis: Focal atrophy of the testis/tubule was observed at increased incidence in high dose male mice (vehicle control, 1/49; low dose, 2/50; high dose, 7/50). This lesion was seen in animals that had underlying disease and was not considered directly related to chemical administration.

TABLE 28. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	75 mg/kg	150 mg/kg
Focal Hyperplasia			
Overall Rates	10/44 (23%)	8/43 (19%)	5/38 (13%)
Adenoma (a)			
Overall Rates	17/44 (39%)	8/43 (19%)	3/38 (8%)
Adjusted Rates	54.6%	46.7%	14.7%
Terminal Rates	12/26 (46%)	5/13 (38%)	1/11 (9%)
Week of First Observation	94	84	47
Life Table Tests	P=0.036N	P=0.459N	P=0.038N
Incidental Tumor Tests	P=0.005N	P=0.158N	P=0.006N

(a) Historical incidence of adenomas or carcinomas (combined) at study laboratory (mean ± SD): 56/248 (23% ± 8%); historical incidence in NTP studies: 257/1,324 (19% ± 9%)

IV. DISCUSSION AND CONCLUSIONS

Study Rationale
Results of Short-Term Studies
Two-Year Studies in Rats
Two-Year Studies in Mice
Comparison of Results with Other Carcinogenicity Studies
Genetic Toxicology
Data Audit
Conclusions

IV. DISCUSSION AND CONCLUSIONS

Study Rationale

Bromodichloromethane (99% pure) was one of three trihalomethanes selected for study in F344/N rats and B6C3F$_1$ mice because chloroform, a related trihalomethane, was found to cause tumors in rodents and no carcinogenicity data were available for these other common water contaminants at the time these studies were started. The chemical was administered by gavage in corn oil. Two other recent carcinogenicity studies of bromodichloromethane allow for a comparison of results after administration by gavage (current NTP studies), drinking water (Tumasonis et al., 1985), and microencapsulation in feed (M. Tobe, National Institute of Hygienic Sciences, Tokyo, Japan, personal communication to J. Dunnick, NTP, 1985).

Results of Short-Term Studies

Bromodichloromethane was administered by gavage 5 days per week to F344/N rats and B6C3F$_1$ mice in a series of single-administration, 14-day, and 13-week studies to determine the affected sites and to set doses for the 2-year studies. These studies showed that the kidney and liver were the affected organs in rodents. In the 14-day studies, male rats at the highest dose (600 mg/kg) and male mice at the two highest doses (150 and 300 mg/kg) had reddened medullae of the kidney. In the 13-week studies, the kidney was again found to be affected in male rats at the highest dose (300 mg/kg) and in male mice at the highest dose (100 mg/kg) but not in female rats or mice. In the 13-week studies, centrilobular degeneration of the liver was seen in male and female rats at 300 mg/kg and in female mice at 200 and 400 mg/kg.

In the 13-week studies, male and female rats received doses of 19-300 mg/kg. Based on deaths at 300 mg/kg, body weight gain depression at 150 and 300 mg/kg in male and female rats, and lesions of the liver and kidney in male rats and of the liver in female rats at 300 mg/kg, doses selected for rats for the 2-year studies were 50 and 100 mg/kg.

In the 13-week studies, male mice received doses of 6.25-100 mg/kg and female mice received doses of 25-400 mg/kg. Body weight gain depression and kidney lesions were observed at 100 mg/kg but not at 50 mg/kg in male mice; in female mice, body weight gain depression and liver lesions were seen at 200 and 400 mg/kg but not at 100 mg/kg. Based on these results, doses selected for the 2-year studies were 25 and 50 mg/kg for male mice and 75 and 150 mg/kg for female mice.

Two-Year Studies in Rats

Final survival of dosed rats was comparable to that of vehicle controls. Body weights of high dose male and female rats were decreased during the last 1.5 years of the study; final mean body weights of males and females were 88% and 79% those of respective vehicle control mean body weights. Final mean body weights of low dose male and female rats were comparable to those of the vehicle controls.

Dose-related nonneoplastic lesions in male rats included cytomegaly and tubular cell hyperplasia in the kidney and necrosis and fatty metamorphosis of the liver and, in female rats, eosinophilic cytoplasmic change, focal cellular change, and fatty metamorphosis in the liver and tubular cell hyperplasia in the kidney. These results confirm the short-term study findings that showed that bromodichloromethane was toxic for the kidney of male rats and for the liver of female rats. The 13-week study results did not predict the kidney toxicity observed in the female rats or the large intestine tumors seen in male and female rats in the 2-year studies.

Administration of bromodichloromethane to male and female rats induced uncommon neoplasms of the large intestine and kidney (see Tables 13 and 14); the historical control incidence of large intestine tumors is less than 0.2% in males and is 0% in females. The intestinal neoplasms diagnosed as adenomatous polyps are similar morphologically to the polypoid adenomas (in contrast to the hyperplastic polyps) seen in humans (Lane et al., 1978). Similarly, invasion of the polyp stalk and submucosa by neoplastic cells marks the progression from the benign to the malignant stage. There is substantial morphologic and empirical evidence that the development of common colon cancer in humans proceeds through a similar sequence of stages.

The spectrum of kidney disease seen in rats after bromodichloromethane administration differs from that seen after animals are exposed to gasoline vapors, light hydrocarbons (Mehlman et al., 1984), 1,4-dichlorobenzene (NTP, 1987a), or dimethyl methylphosphonate (NTP, 1987b). With these compounds, the kidney neoplasms were seen primarily in the male rat; nonneoplastic lesions of the kidney of male rats in the 2-year studies included an increased severity of nephropathy and an increased incidence of mineralization (calcification), and hyaline droplet formation in the kidney was usually seen in the 13-week studies. The kidney neoplasms seen in male and female rats and in male mice administered bromodichloromethane were not accompanied by an increase in nephropathy and mineralization; no hyaline droplet formation in the kidney was seen in the 13-week studies.

Other compounds studied by the NTP which cause kidney lesions include the halogenated hydrocarbons trichloroethylene (NTP, unpublished; NTP, 1987c) and tetrachloroethylene (NTP, 1986). Administration of trichloroethylene by gavage in corn oil or tetrachloroethylene by inhalation caused cytomegaly and karyomegaly of tubular epithelial cells in rats and mice of each sex. Cytomegaly of the kidney was seen only in male rats and male mice given bromodichloromethane by gavage. Whereas renal tubular cell tumors were seen in rats and mice given bromodichloromethane, renal tumors were seen only in rats given the halogenated hydrocarbons.

Miscellaneous lesions noted in rats included increased incidences of skin neoplasms in low dose but not high dose male rats. These lesions were not considered to be clearly compound related.

Decreased incidences of naturally occurring tumors were seen in the adrenal glands of high dose male rats and in the pituitary and mammary glands of female rats; these decreases might be related to decreased body weight in high dose animals.

Two-Year Studies in Mice

Final survival of dosed male mice was comparable to that of vehicle controls. At week 84, survival of female mice was greater than 50% in all dosed groups; after week 84, survival in dosed and vehicle control female mice was reduced (final survival: vehicle control, 26/50; low dose, 13/50; high dose, 15/50). This decreased survival was associated with ovarian abscesses (8/50; 19/47; 18/49). These abscesses were not cultured. In the 2-year pentachloronitrobenzene study conducted at this laboratory (June 1981-May 1983), female mice also had ovarian abscesses, and culture of these lesions showed that Klebsiella sp. were the primary pathogens (NTP, 1987d). The mean body weight of high dose male mice was 5%-9% lower than that of vehicle controls throughout the study; the mean body weight of low dose male mice was comparable to that of vehicle controls. Mean body weights of low and high dose female mice were 9% and 25% lower than those of vehicle controls at the end of the study. No compound-related clinical signs were observed.

Dose-related nonneoplastic lesions included renal cytomegaly, fatty metamorphosis of the liver, and follicular cell hyperplasia of the thyroid gland in male mice and follicular cell hyperplasia of the thyroid gland in female mice.

Bromodichloromethane administration caused compound-related neoplasms in the kidney of male mice and in the liver of female mice (see Tables 26 and 27). Decreased incidences of naturally occurring tumors were seen in the pituitary gland of dosed female mice (see Table 28).

Positive serologic titers for Sendai virus, mouse hepatitis virus, and rat coronavirus were seen in the sentinel animals; however, there was no evidence for an active infection in the study animals, and it is unlikely that these viruses had any impact on the interpretation of the studies.

Comparison of Results with Other Carcinogenicity Studies

Under the conditions of these studies, bromodichloromethane caused the widest spectrum of carcinogenic responses of the trihalomethanes studied in the NCI/NTP program (Table 29) and was associated with the formation of neoplasms of the large intestine and kidney in male and female rats, kidney neoplasms in male mice, and

TABLE 29. SITES OF COMPOUND-RELATED CARCINOGENIC RESPONSES IN THE NCI/NTP TWO-YEAR STUDIES OF TRIHALOMETHANES (a)

Chemical	Dose (mg/kg per day)	Liver	Kidney	Colon/Rectum
Chloroform (b)				
Osborne-Mendel rats				
Male	0, 90, 180	−	+	−
Female	0, 100, 200	−	−	−
$B6C3F_1$ mice				
Male	0, 138, 277	+	−	−
Female	0, 238, 477	+	−	−
Chlorodibromomethane (c)				
F344/N rats				
Male	0, 40, 80	−	−	−
Female	0, 40, 80	−	−	−
$B6C3F_1$ mice				
Male	0, 50, 100	±	−	−
Female	0, 50, 100	+	−	−
Bromodichloromethane				
F344/N rats				
Male	0, 50, 100	−	+	+
Female	0, 50, 100	−	+	+
$B6C3F_1$ mice				
Male	0, 25, 50	−	+	−
Female	0, 75, 100	+	−	−

(a) Carcinogenic response: +, presence of compound-related neoplasms; ±, equivocal evidence for compound-related neoplasms; −, no evidence for compound-related neoplasms.
(b) NCI, 1976a; time-weighted-average dose administered by gavage in corn oil.
(c) NTP, 1985

liver neoplasms in female mice (Table 30). Bromodichloromethane is the only trihalomethane studied to date which caused colon/rectum neoplasms in rodents. Like chloroform, this chemical caused liver neoplasms in female mice and kidney neoplasms in male rats. Chlorodibromomethane caused liver neoplasms in female mice but no neoplasms in rats.

In a drinking-water study in Wistar rats, Tumasonis et al. (1985) estimated that approximately 150 mg/kg per day (females) or 200 mg/kg per day (males) of bromodichloromethane was consumed for the lifetime of the animals, and administration of the chemical at these concentrations resulted in an increase in hepatic neoplastic nodules in female rats. The impact of the relative insolubility of bromodichloromethane in water and its volatile properties were not discussed. In a study in which bromodichloromethane was administered in a microencapsulated form in the diet at concentrations up to 2,200 ppm for 24 months, an increase in liver neoplasms was observed in male and female Wistar rats (M. Tobe, National Institute of Hygienic Sciences, Tokyo, Japan, personal communication to J. Dunnick, NTP, 1985).

A comparison of the carcinogenicity studies of chloroform (doses for male and female Osborne-Mendel rats and $B6C3F_1$ mice given in Table 29) administered by gavage in corn oil (NCI, 1976a) or in drinking water (Jorgenson et al., 1985) showed that chloroform by either route of administration caused kidney neoplasms in male rats; liver neoplasms in female mice were seen only in the gavage study. The time-weighted-average doses of chloroform in the

TABLE 30. COMPOUND-RELATED INCREASED INCIDENCES OF NEOPLASMS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE

RATS			
Male	**Vehicle Control**	**50 mg/kg**	**100 mg/kg**
Large intestine			
Adenomatous polyp	0/50	3/50	33/50
Adenocarcinoma	0/50	11/50	38/50
Adenomatous polyp or adenocarcinoma	0/50	13/50	45/50
Kidney			
Tubular cell adenoma	0/50	1/50	3/50
Tubular cell adenocarcinoma	0/50	0/50	10/50
Tubular cell adenoma or adenocarcinoma	0/50	1/50	13/50
Female	**Vehicle Control**	**50 mg/kg**	**100 mg/kg**
Large intestine			
Adenomatous polyp	0/46	0/50	7/47
Adenocarcinoma	0/46	0/50	6/47
Adenomatous polyp or adenocarcinoma	0/46	0/50	12/47
Kidney			
Tubular cell adenoma	0/50	1/50	6/50
Tubular cell adenocarcinoma	0/50	0/50	9/50
Tubular cell adenoma or adenocarcinoma	0/50	1/50	15/50
MICE			
Male	**Vehicle Control**	**25 mg/kg**	**50 mg/kg**
Kidney			
Tubular cell adenoma	1/49	2/50	6/50
Tubular cell adenocarcinoma	0/49	0/50	4/50
Tubular cell adenoma or adenocarcinoma	1/49	2/50	9/50
Female	**Vehicle Control**	**75 mg/kg**	**150 mg/kg**
Liver			
Hepatocellular adenoma	1/50	13/48	23/50
Hepatocellular carcinoma	2/50	5/48	10/50
Hepatocellular adenoma or carcinoma	3/50	18/48	29/50

Jorgenson study were 0, 19, 38, 81, or 160 mg/kg per day for male rats and 0, 34, 65, 130, or 263 mg/kg per day for female mice.

The results of these different studies suggest that the trihalomethanes are carcinogenic in rodents when given in drinking water, by gavage in corn oil, or in feed. The spectrum of lesions differed somewhat with the chemical, the species, and the experimental design. The male mouse metabolizes bromodichloromethane and the other trihalomethanes at a faster rate than does the male rat (Mink et al., 1986), and this difference may contribute to the species difference in tumor patterns. The mechanism for tumor formation cannot be determined based on the results of these rodent studies. In these studies, neoplasms were seen at dose levels that are higher than the levels of trihalomethanes ordinarily found in most drinking water supplies (USEPA, 1979; Balster and Borzelleca, 1982).

Genetic Toxicology

Bromodichloromethane has been demonstrated to be mutagenic in both in vitro and in vivo test systems. Although bromodichloromethane did not induce gene mutations in microbial plate assays with Salmonella, positive results were observed in bacterial tests both in the presence and absence of metabolic activation when chemical exposure was in a desiccator. In this test system, bromoform and chlorodibromomethane were also mutagenic whereas chloroform was not (Simmon et al., 1977).

The seemingly conflicting results among various microbial tests could be because of the volatile nature of this compound and the consequent difficulties in achieving sufficient exposure. This concept is supported by the studies of Nestmann and Lee (1985) in which mitotic crossing-over was seen when Saccharomyces was incubated with bromodichloromethane for 16 hours, whereas a similar assay by Simmon and Kauhanen (1978) did not demonstrate mitotic crossing-over in another yeast strain incubated with bromodichloromethane for 4 hours.

Bromodichloromethane is also mutagenic to mammalian cells. It induced forward mutations at the thymidine kinase locus in cultured mouse lymphoma cells in the presence of S9. Although results from NTP-sponsored cytogenetic tests in Chinese hamster ovary cells were negative, induction of sister chromatid exchanges in cultured human lymphocytes as well as mouse bone marrow cells treated in vivo is reported in the literature (Morimoto and Koizumi, 1983). Again, these somewhat conflicting responses with mammalian cells in culture may simply be because of a lack of adequate exposure to this volatile chemical or the variable metabolic capacity of the different cell types used in these experiments.

Data Audit

The experimental and tabulated data for the NTP Technical Report on bromodichloromethane were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix H, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenic activity** for male and female F344/N rats and B6C3F$_1$ mice as shown by increased incidences of tubular cell adenomas and adenocarcinomas in the kidney and adenocarcinomas and adenomatous polyps in the large intestine in male and female rats, increased incidences of adenomas and adenocarcinomas in the kidney of male mice, and increased incidences of hepatocellular adenomas and carcinomas in female mice.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.

A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

V. REFERENCES

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

		PAGE
TABLE A1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	75
TABLE A2	INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	78
TABLE A3	ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	84
TABLE A4a	HISTORICAL INCIDENCE OF LARGE INTESTINE TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	90
TABLE A4b	HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	90
TABLE A4c	HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	91
TABLE A4d	HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	92
TABLE A4e	HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	93
TABLE A5	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	94

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		3 (6%)	
Squamous cell carcinoma		3 (6%)	
Basal cell tumor		1 (2%)	
Sebaceous adenoma			1 (2%)
Keratoacanthoma	1 (2%)	1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	2 (4%)	3 (6%)	2 (4%)
Fibrosarcoma	1 (2%)	1 (2%)	1 (2%)
Lipoma		1 (2%)	
Neurofibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma			1 (2%)
Sarcoma, NOS, metastatic		1 (2%)	
Osteosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	8 (16%)	6 (12%)	8 (16%)
#Liver	(50)	(50)	(50)
Leukemia, mononuclear cell		3 (6%)	
#Thymus	(39)	(7)	(42)
Thymoma, benign	1 (3%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Bile duct carcinoma	1 (2%)		
Neoplastic nodule	1 (2%)		3 (6%)
Hepatocellular carcinoma			1 (2%)
Fibrosarcoma		1 (2%)	
#Pancreas	(49)	(50)	(50)
Acinar cell adenoma	5 (10%)	9 (18%)	4 (8%)
Acinar cell carcinoma		1 (2%)	1 (2%)
Mesothelioma, NOS		2 (4%)	
#Forestomach	(49)	(10)	(50)
Squamous cell carcinoma	1 (2%)		
#Duodenum	(49)	(17)	(50)
Adenocarcinoma, NOS		1 (6%)	
#Colon	(50)	(50)	(50)
Adenocarcinoma, NOS		11 (22%)	36 (72%)
Adenomatous polyp, NOS		2 (4%)	29 (58%)
*Rectum	(50)	(50)	(50)
Adenocarcinoma, NOS			6 (12%)
Adenomatous polyp, NOS		1 (2%)	4 (8%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Adenocarcinoma, NOS, unclear prim/meta			1 (2%)
Tubular cell adenoma		1 (2%)	3 (6%)
Tubular cell adenocarcinoma			10 (20%)
Sarcoma, NOS		1 (2%)	
Fibrosarcoma		1 (2%)	
#Urinary bladder	(49)	(12)	(48)
Transitional cell papilloma	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(13)	(48)
Carcinoma, NOS	4 (8%)	2 (15%)	2 (4%)
Adenoma, NOS	13 (27%)	6 (46%)	12 (25%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma		1 (2%)	1 (2%)
Cortical carcinoma			1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	17 (34%)	13 (26%)	3 (6%)
Pheochromocytoma, malignant	1 (2%)	2 (4%)	2 (4%)
#Thyroid	(50)	(12)	(50)
Follicular cell adenoma		1 (8%)	
Follicular cell carcinoma		1 (8%)	
C-cell adenoma	1 (2%)		2 (4%)
C-cell carcinoma	1 (2%)	1 (8%)	1 (2%)
#Pancreatic islets	(49)	(50)	(50)
Islet cell adenoma	2 (4%)	1 (2%)	
Islet cell carcinoma	1 (2%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	2 (4%)		
Fibroadenoma		3 (6%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	5 (10%)	
Squamous cell carcinoma		1 (2%)	
Adenoma, NOS		1 (2%)	
#Testis	(50)	(47)	(50)
Interstitial cell tumor	41 (82%)	43 (91%)	45 (90%)
*Scrotum	(50)	(50)	(50)
Mesothelioma, NOS		2 (4%)	
NERVOUS SYSTEM			
#Cerebrum	(50)	(8)	(50)
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
*Eyelid	(50)	(50)	(50)
Fibroma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Sebaceous adenocarcinoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Lipoma		1 (2%)	
*Mesentery	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		3 (6%)	3 (6%)
Mesothelioma, malignant		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Tubular cell adenocarcinoma, metastatic			1 (2%)
Mesothelioma, NOS	2 (4%)		
Lower leg			
Osteosarcoma	1		
Omentum			
Sarcoma, NOS, metastatic		1	
Mesothelioma, NOS			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	3	6
Moribund sacrifice	20	10	16
Terminal sacrifice	27	36	28
Accidentally killed, nda		1	
TUMOR SUMMARY			
Total animals with primary tumors**	48	48	49
Total primary tumors	113	146	188
Total animals with benign tumors	43	47	49
Total benign tumors	85	94	109
Total animals with malignant tumors	22	27	43
Total malignant tumors	25	44	71
Total animals with secondary tumors##	1	1	1
Total secondary tumors	1	2	1
Total animals with tumors uncertain-- benign or malignant	3	3	5
Total uncertain tumors	3	8	7
Total animals with tumors uncertain-- primary or metastatic			1
Total uncertain tumors			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.

** Primary tumors: all tumors except secondary tumors

# Number of animals examined microscopically at this site

## Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: VEHICLE CONTROL

ANIMAL NUMBER	003	008	011	017	024	035	048	045	016	036	040	018	004	005	021	022	030	025	037	041	046	006	001	010	015
WEEKS ON STUDY	053	055	060	065	077	079	081	085	089	089	091	093	096	096	096	096	096	097	097	098	098	102	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma				X																					
Neurofibrosarcoma																			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Thymus	-	+	+	+	+	-	+	+	-	+	+	+	+	+	-	-	-	-	+	+	-	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma																									
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	-	-	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS			X										X												
Adenoma, NOS												X			X		X		X					X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X			X							X	X			X					X
Pheochromocytoma, malignant																							X		
Thyroid	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	-	-	-	+	-	-	+	+	+	+	-	-	+	+	-	+	+	-	-	+	-	+	-	-	-
Pancreatic islets	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X						
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	N	N	N	N	N	+	+	+	+	N	+	N	+	N	N	N	+	N	N	N	+
Adenocarcinoma, NOS												X													
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor					X	X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS					X												X								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																						X			
SPECIAL SENSE ORGANS																									
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibroma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS										X	X														
Leukemia, mononuclear cell	X								X							X		X							
Lower leg, NOS																									
Osteosarcoma								X																	

+ Tissue examined microscopically
- Required tissue not examined microscopically
X Tumor incidence
N Necropsy, no autolysis, no microscopic examination
S Animal missexed

No tissue information submitted
C Necropsy, no histology due to protocol
A Autolysis
M Animal missing
B No necropsy performed

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	019	025	042	044	002	007	009	012	013	014	018	020	027	028	029	030	031	032	033	034	038	039	043	047	049	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma														X												1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma	X													X												2
Fibrosarcoma																										1
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	-	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Thymoma, benign																	X									1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct carcinoma					X																					1
Neoplastic nodule																						X				1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma				X							X		X	X							X					5
Esophagus	+	+	-	+	+	-	+	-	-	+	+	+	+	+	+	+	+	-	+	+	-	+	+	-	-	37
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma							X																			1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell papilloma																				X						1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS		X																						X		4
Adenoma, NOS				X	X	X			X			X				X				X						13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X	X	X		X		X					X		X	X	X					X		X		17
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell adenoma																							X			1
C cell carcinoma																		X								1
Parathyroid	-	-	-	+	-	-	+	+	-	-	+	-	-	+	-	-	+	-	-	-	-	-	+	+	+	21
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma			X																							2
Islet cell carcinoma						X																				1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																X										2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibroma																							X			1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										2
Leukemia, mononuclear cell		X				X										X						X				8
Lower leg, NOS																										
Osteosarcoma																										1

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: LOW DOSE

ANIMAL NUMBER	046	029	045	039	020	035	003	031	004	022	042	0[illegible]4	011	046	001	002	005	006	007	008	009	010	012	013	014
WEEKS ON STUDY	033	060	069	075	07[illegible]	086	088	089	095	096	098	100	101	10[illegible]	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	N	+	N	+	N	N	+	N	N	N	+	+	N	N	N	N
Squamous cell papilloma																				X					
Squamous cell carcinoma																X									
Basal cell tumor																									
Keratoacanthoma									X																
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	N	+	N	N	+	N	N	N	+	+	N	N	N	N
Fibroma					X																				
Fibrosarcoma											X														
Lipoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X	X						
Sarcoma, NOS, metastatic	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																X									
Leukemia, mononuclear cell																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma									X	X							X				X				
Acinar cell carcinoma												X													
Mesothelioma, NOS																				X		X			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic	X																								
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS						X				X							X	X	X						
Adenomatous polyp, NOS													X												
Rectum	N	N	N	N	+	+	N	N	+	+	+	+	+	+	N	N	+	+	+	N	+	+	+	+	+
Adenomatous polyp, NOS									X																
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Sarcoma, NOS	X																								
Fibrosarcoma																X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X														X						
Adenoma, NOS				X				X					X												
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																		X							
Pheochromocytoma											X		X			X	X			X					X
Pheochromocytoma, malignant								X					X												
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma						X																			
Follicular cell carcinoma																									
C-cell carcinoma																						X			
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma							X																		
Islet cell carcinoma																			X						
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	+	+	N	N	N	N	N	N	N
Fibroadenoma																	X	X							
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X	X		X	X	X	X	X		X	X	X		X	X	X		X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS									X							X						X			
Squamous cell carcinoma																									
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lipoma																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Mesothelioma, NOS																	X			X		X			
Mesothelioma, malignant																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																				X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell						X	X			X															
Scrotum, NOS																									
Mesothelioma, NOS																				X		X			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	015	016	017	018	019	021	023	024	025	026	027	028	030	032	033	036	037	038	040	041	043	044	047	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	N	N	N	+	N	N	N	N	N	+	+	+	+	N	+	N	N	N	N	N	+	N	*50
Squamous cell papilloma	X						X																			3
Squamous cell carcinoma			X												X											3
Basal cell tumor													X													1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	N	N	N	+	N	N	N	N	N	+	+	+	+	N	+	N	N	N	N	N	+	N	*50
Fibroma		X													X											3
Fibrosarcoma																										1
Lipoma																		X								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Sarcoma, NOS, metastatic																										1
Trachea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	12
HEMATOPOIETIC SYSTEM																										
Bone marrow	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	8
Spleen	-	+	-	+	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+	+	+	23
Lymph nodes	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	18
Thymus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-	-	7
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Leukemia, mononuclear cell													X						X			X				3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma						X	X				X					X								X		9
Acinar cell carcinoma																										1
Mesothelioma, NOS																										2
Esophagus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	10
Stomach	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10
Sarcoma, NOS, metastatic																										1
Small intestine	-	-	-	-	-	+	-	+	-	+	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	17
Adenocarcinoma, NOS						X																				1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS			X				X				X		X						X				X			11
Adenomatous polyp, NOS							X																			2
Rectum	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenomatous polyp, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																							X			1
Sarcoma, NOS																										1
Fibrosarcoma																										1
Urinary bladder	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	12
ENDOCRINE SYSTEM																										
Pituitary	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	+	-	-	-	-	13
Carcinoma, NOS																										2
Adenoma, NOS														X	X						X					6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma							X			X			X		X					X		X	X			13
Pheochromocytoma, malignant																										2
Thyroid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	12
Follicular cell adenoma																										1
Follicular cell carcinoma																								X		1
C-cell carcinoma																										1
Parathyroid	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	6
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
Islet cell carcinoma													X													2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Fibroadenoma																	X									3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	43
Prostate	+	+	+	+	-	+	+	-	-	-	-	+	+	+	+	+	+	-	-	-	+	-	+	-	+	34
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS						X			X																	5
Squamous cell carcinoma															X											1
Adenoma, NOS										X																1
NERVOUS SYSTEM																										
Brain	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Lipoma																									X	1
Tunica vaginalis	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50
Mesothelioma, NOS																										3
Mesothelioma, malignant															X											1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell			X					X															X			6
Scrotum, NOS																										
Mesothelioma, NOS																										2

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: HIGH DOSE

ANIMAL NUMBER	029	023	045	001	012	031	022	009	024	035	002	007	017	019	030	037	004	016	046	047	006	040	003	005	008
WEEKS ON STUDY	049	051	057	070	079	080	082	085	089	089	091	094	095	096	096	096	097	097	097	097	101	101	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																	X								
Fibrosarcoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Hepatocellular carcinoma														X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Acinar cell carcinoma																									
Esophagus	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS						X		X	X	X	X		X	X	X	X			X	X		X	X	X	
Adenomatous polyp, NOS	X	X		X			X	X			X	X				X		X	X	X		X	X	X	X
Rectum	N	N	N	N	+	N	N	N	N	N	+	+	+	+	+	+	+	+	N	+	N	+	+	N	+
Adenocarcinoma, NOS												X								X					X
Adenomatous polyp, NOS																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, unclear primary/metastatic																									
Tubular cell adenoma																X					X				
Tubular cell adenocarcinoma										X										X					
Urinary bladder	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS						X						X			X									X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Cortical carcinoma																									
Pheochromocytoma									X									X							
Pheochromocytoma, malignant				X																				X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell adenoma																									
C cell carcinoma																								X	
Parathyroid	−	+	+	−	−	−	+	−	−	−	+	+	+	−	−	+	−	−	+	+	−	+	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	+	+	+	N	N	N	N	+	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Sebaceous adenocarcinoma													X												
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Tubular cell adenocarcinoma, metastatic										X															
Leukemia, mononuclear cell	X						X				X							X							

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	010	011	013	014	015	018	020	021	025	026	027	028	032	033	034	036	038	039	041	042	043	044	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma						X																				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma									X																	2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X					X									3
Alveolar/bronchiolar carcinoma	X																									1
Trachea	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule		X																			X			X		3
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																	X		X	X		X				4
Acinar cell carcinoma																					X					1
Esophagus	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	41
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, NOS																	X									1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS		X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	38
Adenomatous polyp, NOS		X		X		X	X	X		X	X			X	X	X	X	X		X			X			29
Rectum	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Adenocarcinoma, NOS					X						X					X										6
Adenomatous polyp, NOS	X				X							X	X													4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, uncl prim/meta						X																				1
Tubular cell adenoma																	X									3
Tubular cell adenocarcinoma	X	X						X			X			X		X						X	X			10
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4.
Carcinoma, NOS	X																			X						2
Adenoma, NOS		X		X								X		X				X				X		X		12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																								X		1
Cortical carcinoma	X																									1
Pheochromocytoma																X										3
Pheochromocytoma, malignant																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell adenoma						X										X										2
C cell carcinoma																										1
Parathyroid	-	+	-	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	+	+	+	-	-	27
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sebaceous adenocarcinoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																	X							X	X	3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Tubular cell adenocarcinoma, metas																										1
Leukemia, mononuclear cell														X			X				X		X			8

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	8.3%	0.0%
Terminal Rates (c)	0/28 (0%)	3/36 (8%)	0/28 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.646	P=0.168	(e)
Incidental Tumor Tests (d)	P=0.646	P=0.168	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(e)
Skin: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	8.3%	0.0%
Terminal Rates (c)	0/28 (0%)	3/36 (8%)	0/28 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.646	P=0.168	(e)
Incidental Tumor Tests (d)	P=0.646	P=0.168	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(e)
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	6/50 (12%)	0/50 (0%)
Adjusted Rates (b)	0.0%	16.7%	0.0%
Terminal Rates (c)	0/28 (0%)	6/36 (17%)	0/28 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.606	P=0.034	(e)
Incidental Tumor Tests (d)	P=0.606	P=0.034	(e)
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Test (d)		P=0.013	(e)
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	7.1%	7.6%	6.4%
Terminal Rates (c)	2/28 (7%)	2/36 (6%)	1/28 (4%)
Week of First Observation	104	76	97
Life Table Tests (d)	P=0.594N	P=0.591	P=0.691N
Incidental Tumor Tests (d)	P=0.544	P=0.571	P=0.694
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.500	P=0.691
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	9.1%	9.9%	9.9%
Terminal Rates (c)	2/28 (7%)	2/36 (6%)	2/28 (7%)
Week of First Observation	65	76	97
Life Table Tests (d)	P=0.580N	P=0.584	P=0.659N
Incidental Tumor Tests (d)	P=0.493	P=0.497	P=0.595
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.500	P=0.661
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	11.9%	9.9%	9.9%
Terminal Rates (c)	2/28 (7%)	2/36 (6%)	2/28 (7%)
Week of First Observation	65	76	97
Life Table Tests (d)	P=0.422N	P=0.553N	P=0.495N
Incidental Tumor Tests (d)	P=0.507N	P=0.601	P=0.567N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test (d)		P=0.643	P=0.500N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	5.6%	9.7%
Terminal Rates (c)	0/28 (0%)	2/36 (6%)	2/28 (7%)
Week of First Observation		104	96
Life Table Tests (d)	P=0.073	P=0.295	P=0.120
Incidental Tumor Tests (d)	P=0.079	P=0.295	P=0.123
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.247	P=0.121
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	0.0%	5.6%	13.1%
Terminal Rates (c)	0/28 (0%)	2/36 (6%)	3/28 (11%)
Week of First Observation		104	96
Life Table Tests (d)	P=0.031	P=0.295	P=0.062
Incidental Tumor Tests (d)	P=0.034	P=0.295	P=0.064
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		P=0.247	P=0.059
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	8/50 (16%)	(f) 9/50 (18%)	8/50 (16%)
Adjusted Rates (b)	22.6%		22.3%
Terminal Rates (c)	4/28 (14%)		4/28 (14%)
Week of First Observation	53		49
Life Table Test (d)			P=0.601N
Incidental Tumor Test (d)			P=0.522N
Fisher Exact Test (d)			P=0.607N
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	3.6%	0.0%	10.7%
Terminal Rates (c)	1/28 (4%)	0/36 (0%)	3/28 (11%)
Week of First Observation	105		104
Life Table Tests (d)	P=0.164	P=0.450N	P=0.304
Incidental Tumor Tests (d)	P=0.164	P=0.450N	P=0.304
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test (d)		P=0.500N	P=0.309
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	3.6%	0.0%	13.1%
Terminal Rates (c)	1/28 (4%)	0/36 (0%)	3/28 (11%)
Week of First Observation	105		96
Life Table Tests (d)	P=0.074	P=0.450N	P=0.179
Incidental Tumor Tests (d)	P=0.079	P=0.450N	P=0.180
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.500N	P=0.181
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	5/49 (10%)	9/50 (18%)	4/50 (8%)
Adjusted Rates (b)	17.9%	23.3%	14.3%
Terminal Rates (c)	5/28 (18%)	7/36 (19%)	4/28 (14%)
Week of First Observation	104	95	104
Life Table Tests (d)	P=0.436N	P=0.340	P=0.500N
Incidental Tumor Tests (d)	P=0.436N	P=0.269	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test (d)		P=0.205	P=0.487N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Pancreas: Acinar Cell Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	10/50 (20%)	5/50 (10%)
Adjusted Rates (b)	17.9%	25.2%	17.9%
Terminal Rates (c)	5/28 (18%)	7/36 (19%)	5/28 (18%)
Week of First Observation	104	95	104
Life Table Tests (d)	P=0.561N	P=0.263	P=0.635
Incidental Tumor Tests (d)	P=0.561	P=0.166	P=0.635
Cochran-Armitage Trend Test (d)	P=0.543N		
Fisher Exact Test (d)		P=0.140	P=0.617N
Large Intestine: Adenomatous Polyp			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	33/50 (66%)
Adjusted Rates (b)	0.0%	7.6%	81.7%
Terminal Rates (c)	0/28 (0%)	1/36 (3%)	21/28 (75%)
Week of First Observation		95	49
Life Table Tests (d)	P<0.001	P=0.163	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.067	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.121	P<0.001
Large Intestine: Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	11/50 (22%)	38/50 (76%)
Adjusted Rates (b)	0.0%	28.5%	92.5%
Terminal Rates (c)	0/28 (0%)	9/36 (25%)	25/28 (89%)
Week of First Observation		86	80
Life Table Tests (d)	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Large Intestine: Adenomatous Polyp or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	13/50 (26%)	45/50 (90%)
Adjusted Rates (b)	0.0%	32.0%	97.8%
Terminal Rates (c)	0/28 (0%)	9/36 (25%)	27/28 (96%)
Week of First Observation		86	49
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Kidney: Tubular Cell Adenoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.8%	9.3%
Terminal Rates (c)	0/28 (0%)	1/36 (3%)	1/28 (4%)
Week of First Observation		104	96
Life Table Tests (d)	P=0.056	P=0.550	P=0.125
Incidental Tumor Tests (d)	P=0.065	P=0.550	P=0.120
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Kidney: Tubular Cell Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	10/50 (20%)
Adjusted Rates (b)	0.0%	0.0%	32.3%
Terminal Rates (c)	0/28 (0%)	0/36 (0%)	8/28 (29%)
Week of First Observation			89
Life Table Tests (d)	P<0.001	(e)	P=0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		(e)	P<0.001

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	13/50 (26%)
Adjusted Rates (b)	0.0%	2.8%	39.5%
Terminal Rates (c)	0/28 (0%)	1/36 (3%)	9/28 (32%)
Week of First Observation		104	89
Life Table Tests (d)	P<0.001	P=0.550	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.550	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.500	P<0.001
Pituitary Gland: Adenoma			
Overall Rates (a)	13/48 (27%)	(g) 6/13 (46%)	12/48 (25%)
Adjusted Rates (b)	39.3%		38.2%
Terminal Rates (c)	9/28 (32%)		9/27 (33%)
Week of First Observation	93		80
Life Table Test (d)			P=0.530N
Incidental Tumor Test (d)			P=0.515N
Fisher Exact Test (d)			P=0.500N
Pituitary Gland: Carcinoma			
Overall Rates (a)	4/48 (8%)	(g) 2/13 (15%)	2/48 (4%)
Adjusted Rates (b)	11.5%		7.4%
Terminal Rates (c)	2/28 (7%)		2/27 (7%)
Week of First Observation	60		104
Life Table Test (d)			P=0.353N
Incidental Tumor Test (d)			P=0.444N
Fisher Exact Test (d)			P=0.339N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	17/48 (35%)	(g) 8/13 (62%)	14/48 (29%)
Adjusted Rates (b)	48.3%		45.1%
Terminal Rates (c)	11/28 (39%)		11/27 (41%)
Week of First Observation	60		80
Life Table Test (d)			P=0.369N
Incidental Tumor Test (d)			P=0.397N
Fisher Exact Test (d)			P=0.332N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	17/50 (34%)	13/50 (26%)	3/50 (6%)
Adjusted Rates (b)	50.0%	34.0%	8.6%
Terminal Rates (c)	12/28 (43%)	11/35 (31%)	1/28 (4%)
Week of First Observation	79	96	89
Life Table Tests (d)	P<0.001N	P=0.089N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.200N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.257N	P<0.001N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	18/50 (36%)	14/50 (28%)	5/50 (10%)
Adjusted Rates (b)	53.1%	35.6%	13.9%
Terminal Rates (c)	13/28 (46%)	11/36 (31%)	2/28 (7%)
Week of First Observation	79	89	70
Life Table Tests (d)	P=0.002N	P=0.091N	P=0.003N
Incidental Tumor Tests (d)	P=0.002N	P=0.217N	P=0.003N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.260N	P=0.002N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	(g) 1/12 (8%)	3/50 (6%)
Adjusted Rates (b)	7.1%		10.7%
Terminal Rates (c)	2/28 (7%)		3/28 (11%)
Week of First Observation	105		104
Life Table Test (d)			P=0.500
Incidental Tumor Test (d)			P=0.500
Fisher Exact Test (d)			P=0.500
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	10.0%	7.7%	0.0%
Terminal Rates (c)	2/28 (7%)	2/36 (6%)	0/25 (0%)
Week of First Observation	97	88	
Life Table Tests (d)	P=0.094N	P=0.565N	P=0.121N
Incidental Tumor Tests (d)	P=0.092N	P=0.657	P=0.123N
Cochran-Armitage Trend Test (d)	P=0.097N		
Fisher Exact Test (d)		P=0.652N	P=0.118N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	8.3%	0.0%
Terminal Rates (c)	0/28 (0%)	3/36 (8%)	0/28 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.646	P=0.168	(e)
Incidental Tumor Tests (d)	P=0.646	P=0.168	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(e)
Preputial Gland: Carcinoma or Squamous Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	0/50 (0%)
Adjusted Rates (b)	4.7%	15.9%	0.0%
Terminal Rates (c)	0/28 (0%)	5/36 (14%)	0/28 (0%)
Week of First Observation	77	95	
Life Table Tests (d)	P=0.250N	P=0.202	P=0.243N
Incidental Tumor Tests (d)	P=0.291N	P=0.128	P=0.336N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test (d)		P=0.134	P=0.247N
Preputial Gland: Adenoma, Carcinoma, or Squamous Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	0/50 (0%)
Adjusted Rates (b)	4.7%	18.7%	0.0%
Terminal Rates (c)	0/28 (0%)	6/36 (17%)	0/28 (0%)
Week of First Observation	77	95	
Life Table Tests (d)	P=0.261N	P=0.137	P=0.243N
Incidental Tumor Tests (d)	P=0.301N	P=0.083	P=0.336N
Cochran-Armitage Trend Test (d)	P=0.264N		
Fisher Exact Test (d)		P=0.080	P=0.247N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	41/50 (82%)	43/47 (91%)	45/50 (90%)
Adjusted Rates (b)	97.6%	97.7%	100%
Terminal Rates (c)	27/28 (96%)	33/34 (97%)	28/28 (100%)
Week of First Observation	77	69	70
Life Table Tests (d)	P=0.254	P=0.211N	P=0.298
Incidental Tumor Tests (d)	P=0.073	P=0.125	P=0.120
Cochran-Armitage Trend Test (d)	P=0.143		
Fisher Exact Test (d)		P=0.141	P=0.194

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Tunica Vaginalis: Mesothelioma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	0.0%	8.3%	10.7%
Terminal Rates (c)	0/28 (0%)	3/36 (8%)	3/28 (11%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.089	P=0.168	P=0.120
Incidental Tumor Tests (d)	P=0.089	P=0.168	P=0.120
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.121	P=0.121
All Sites: Mesothelioma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	4.8%	11.1%	10.7%
Terminal Rates (c)	0/28 (0%)	4/36 (11%)	3/28 (11%)
Week of First Observation	89	104	104
Life Table Tests (d)	P=0.414	P=0.423	P=0.500
Incidental Tumor Tests (d)	P=0.436	P=0.306	P=0.528
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.339	P=0.500

(a) Number of tumor-bearing animals/number of animals examined at the site

(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality

(c) Observed tumor incidence at terminal kill

(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

(e) No P value is reported because no tumors were observed in the dosed and vehicle control groups.

(f) Only 23 spleens were examined.

(g) Incomplete sampling of tissue

TABLE A4a. HISTORICAL INCIDENCE OF LARGE INTESTINE TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Historical Incidence at EG&G Mason Research Institute

No colon or rectum tumors have been observed in 250 male vehicle control rats.

Overall Historical Incidence	No. Examined	No. of Tumors	Diagnosis
Colon	1,390	1	Adenomatous polyp
		1	Cystadenoma
		1	Adenocarcinoma
TOTAL		(b) 3 (0.2%)	
Rectum	1,390	0	

(a) Data as of August 30, 1985, for studies of at least 104 weeks; large intestine includes both colon and rectum.
(b) All three large intestine tumors were observed in the ethyl acrylate study.

TABLE A4b. HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. Examined	No. of Tumors	Diagnosis
Historical Incidence at EG&G Mason Research Institute			
	250	(b) 1 (0.4%)	Tubular cell adenocarcinoma
Overall Historical Incidence			
		3	Tubular cell adenoma
		2	Adenocarcinoma, NOS
		3	Tubular cell adenocarcinoma
TOTAL	1,448	8 (0.6%)	

(a) Data as of August 30, 1985, for studies of at least 104 weeks. No more than one tumor has been observed in any vehicle control group.
(b) Observed in the diglycidyl resorcinol ether study

TABLE A4c. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls Papilloma	 Carcinoma	 Papilloma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	1/50	0/50	1/50
Diglycidyl resorcinol ether	0/50	1/50	1/50
1,2-Dichloropropane	2/50	3/50	5/50
Chlorodibromomethane	0/50	0/50	0/50
n-Butyl chloride	0/50	0/50	0/50
TOTAL	3/250 (1.2%)	4/250 (1.6%)	7/250 (2.8%)
SD (b)	1.79%	2.61%	4.15%
Range (c)			
High	2/50	3/50	5/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	27/1,450 (1.9%)	11/1,450 (0.8%)	38/1,450 (2.6%)
SD (b)	2.39%	1.35%	2.88%
Range (c)			
High	4/50	3/50	5/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks

(b) Standard deviation

(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4d. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	3/50	1/50	4/50
Diglycidyl resorcinol ether	2/50	0/50	2/50
1,2-Dichloropropane	2/49	0/49	2/49
Chlorodibromomethane	1/50	2/50	3/50
n-Butyl chloride	1/50	0/50	1/50
TOTAL	9/249 (3.6%)	3/249 (1.2%)	12/249 (4.8%)
SD (b)	1.68%	1.79%	2.27%
Range (c)			
High	3/50	2/50	4/50
Low	1/50	0/50	1/50
Overall Historical Incidence			
TOTAL	31/1,448 (2.1%)	16/1,448 (1.1%)	47/1,448 (3.2%)
SD (b)	2.20%	1.66%	2.85%
Range (c)			
High	4/50	3/50	4/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks

(b) Standard deviation

(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4e. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	11/50	1/50	12/50
Diglycidyl resorcinol ether	11/50	1/50	11/50
1,2-Dichloropropane	11/50	0/50	11/50
Chlorodibromomethane	7/50	1/50	8/50
n-Butyl chloride	14/50	1/50	15/50
TOTAL	54/250 (21.6%)	4/250 (1.6%)	57/250 (22.8%)
SD (b)	4.98%	0.89%	5.02%
Range (c)			
High	14/50	1/50	15/50
Low	7/50	0/50	8/50
Overall Historical Incidence			
TOTAL	338/1,442 (23.4%)	13/1,442 (0.9%)	347/1,442 (24.1%)
SD (b)	8.72%	1.27%	8.66%
Range (c)			
High	20/49	2/50	20/49
Low	2/50	0/50	2/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks

(b) Standard deviation

(c) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)	1 (2%)	
Abscess, NOS		1 (2%)	
Hyperplasia, NOS	1 (2%)		
Hyperkeratosis	1 (2%)	1 (2%)	
Acanthosis		1 (2%)	
Parakeratosis		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Steatitis	1 (2%)		
Abscess, NOS		2 (4%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	5 (10%)
Inflammation, chronic	7 (14%)	1 (2%)	9 (18%)
#Lung	(50)	(50)	(50)
Congestion, NOS	1 (2%)	19 (38%)	
Hemorrhage		1 (2%)	
Bronchopneumonia, NOS	1 (2%)		
Inflammation, interstitial		1 (2%)	
Bronchopneumonia, acute			2 (4%)
Pneumonia, interstitial chronic			3 (6%)
Inflammation, chronic focal			2 (4%)
Granuloma, NOS	1 (2%)		1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)		2 (4%)
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis			1 (2%)
HEMATOPOIETIC SYSTEM			
#Spleen	(50)	(23)	(50)
Hemorrhage	1 (2%)		
Necrosis, NOS			1 (2%)
Hemosiderosis		2 (9%)	
Hyperplasia, reticulum cell		1 (4%)	
Hematopoiesis		2 (9%)	
#Mandibular lymph node	(48)	(16)	(49)
Cyst, NOS	2 (4%)	1 (6%)	3 (6%)
Inflammation, acute			1 (2%)
Hyperplasia, plasma cell	1 (2%)	2 (13%)	1 (2%)
Hyperplasia, lymphoid		1 (6%)	
#Pancreatic lymph node	(48)	(16)	(49)
Cyst, NOS			1 (2%)
Pigmentation, NOS		1 (6%)	
#Inguinal lymph node	(48)	(16)	(49)
Hyperplasia, plasma cell			1 (2%)
CIRCULATORY SYSTEM			
#Lung	(50)	(50)	(50)
Perivasculitis		1 (2%)	
#Heart	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
Inflammation, chronic focal		1 (2%)	
Necrosis, focal	1 (2%)		
Calcification, focal			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#Myocardium	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
Degeneration, NOS	44 (88%)	43 (86%)	33 (66%)
*Artery	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
Necrosis, NOS		1 (2%)	
#Pancreas	(49)	(50)	(50)
Periarteritis	1 (2%)	2 (4%)	
DIGESTIVE SYSTEM			
*Lip	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
#Salivary gland	(50)	(12)	(49)
Cyst, NOS		1 (8%)	
Inflammation, suppurative			1 (2%)
Inflammation, chronic		1 (8%)	
Metaplasia, squamous			2 (4%)
#Liver	(50)	(50)	(50)
Congenital malformation, NOS	2 (4%)	1 (2%)	
Inflammation, acute focal	1 (2%)		
Inflammation, chronic focal	1 (2%)	4 (8%)	
Granuloma, NOS	1 (2%)		1 (2%)
Cholangiofibrosis			2 (4%)
Degeneration, cystic	1 (2%)		
Necrosis, focal	1 (2%)	3 (6%)	1 (2%)
Metamorphosis, fatty	36 (72%)	48 (96%)	47 (94%)
Cytoplasmic vacuolization			1 (2%)
Basophilic cyto change	38 (76%)	23 (46%)	17 (34%)
Ground glass cyto change	1 (2%)	3 (6%)	
Focal cellular change			1 (2%)
Eosinophilic cyto change		1 (2%)	2 (4%)
Clear cell change	23 (46%)	21 (42%)	24 (48%)
Angiectasis	1 (2%)		
Nodular regeneration			1 (2%)
#Portal tract	(50)	(50)	(50)
Sclerosis	1 (2%)	1 (2%)	1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	4 (8%)
Necrosis, diffuse			1 (2%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	42 (84%)	48 (96%)	44 (88%)
#Pancreas	(49)	(50)	(50)
Inflammation, chronic focal	4 (8%)	1 (2%)	2 (4%)
Inflammation, chronic diffuse		1 (2%)	
Pigmentation, NOS		1 (2%)	
#Pancreatic acinus	(49)	(50)	(50)
Atrophy, focal	8 (16%)	4 (8%)	4 (8%)
Atrophy, diffuse		1 (2%)	
Hyperplasia, focal	4 (8%)	12 (24%)	4 (8%)
#Periesophageal tissue	(37)	(10)	(41)
Inflammation, acute	1 (3%)		
#Stomach	(49)	(10)	(50)
Parasitism	1 (2%)		
#Glandular stomach	(49)	(10)	(50)
Inflammation, chronic focal	1 (2%)		1 (2%)
Calcification, NOS	1 (2%)		
Calcification, focal	1 (2%))		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(49)	(10)	(50)
Ulcer, NOS	2 (4%)		2 (4%)
Inflammation, acute	3 (6%)		1 (2%)
Inflammation, acute/chronic			1 (2%)
Calcification, focal	1 (2%)		
Epithelial hyperplasia			1 (2%)
Hyperkeratosis			1 (2%)
Acanthosis	1 (2%)		1 (2%
#Colon	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
Inflammation, acute			1 (2%)
Parasitism	9 (18%)	11 (22%)	5 (10%)
#Colonic mucosa	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
#Colonic submucosa	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
Calcification, NOS		1 (2%)	
#Cecum	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
Inflammation, chronic			1 (2%)
Necrosis, NOS		1 (2%)	
Calcification, NOS		1 (2%)	
*Rectum	(50)	(50)	(50)
Parasitism	3 (6%)	4 (8%)	3 (6%)
Hyperplasia, epithelial			2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis		1 (2%)	
Nephrosis, NOS	45 (90%)	49 (98%)	47 (94%)
#Kidney/cortex	(50)	(50)	(50)
Inflammation, chronic focal			2 (4%)
Scar			1 (2%)
#Kidney/medulla	(50)	(50)	(50)
Calculus, microscopic examination			1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Necrosis, cortical			1 (2%)
Calcification, NOS	1 (2%)		
Pigmentation, NOS	1 (2%)	2 (4%)	
Cytoplasmic vacuolization		1 (2%)	
Cytomegaly		18 (36%)	44 (88%)
Hyperplasia, tubular cell			3 (6%)
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, suppurative		2 (4%)	
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(49)	(12)	(48)
Inflammation, suppurative		1 (8%)	
Inflammation, acute hemorrhagic		1 (8%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(13)	(48)
Cyst, NOS	1 (2%)		1 (2%)
Atypia, NOS	1 (2%)		
Cytomegaly	1 (2%)		
Hyperplasia, focal	6 (13%)		5 (10%)
#Adrenal	(50)	(50)	(50)
Metamorphosis, fatty		1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(50)	(50)
Degeneration, NOS	10 (20%)	2 (4%)	3 (6%)
Metamorphosis, fatty	1 (2%)	2 (4%)	
Hyperplasia, focal	3 (6%)	4 (8%)	3 (6%)
Angiectasis	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	9 (18%)	7 (14%)	10 (20%)
Angiectasis	1 (2%)		
#Thyroid	(50)	(12)	(50)
Hyperplasia, C-cell	3 (6%)	1 (8%)	2 (4%)
Hyperplasia, follicular cell	1 (2%)		
#Parathyroid	(21)	(6)	(27)
Hyperplasia, NOS	1 (5%)		
#Pancreatic islets	(49)	(50)	(50)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	4 (8%)	1 (2%)	
*Preputial gland	(50)	(50)	(50)
Inflammation, suppurative		6 (12%)	3 (6%)
Inflammation, chronic	26 (52%)	23 (46%)	13 (26%)
Granuloma, NOS	1 (2%)		
#Prostate	(49)	(34)	(49)
Inflammation, suppurative	8 (16%)	3 (9%)	7 (14%)
Inflammation, chronic focal			2 (4%)
Inflammation, chronic diffuse	1 (2%)	1 (3%)	
Hyperplasia, focal			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Retention of content		1 (2%)	
Inflammation, suppurative		2 (4%)	
#Testis	(50)	(47)	(50)
Atrophy, NOS			3 (6%)
Hyperplasia, interstitial cell	6 (12%)	6 (13%)	10 (20%)
#Testis/tubule	(50)	(47)	(50)
Degeneration, NOS	3 (6%)	4 (9%)	1 (2%)
*Epididymis	(50)	(50)	(50)
Retention of content			3 (6%)
Inflammation, suppurative		1 (2%)	
Granuloma, spermatic			4 (8%)
*Scrotum	(50)	(50)	(50)
Necrosis, fat	1 (2%)	2 (4%)	
NERVOUS SYSTEM			
#Cerebrum	(50)	(8)	(50)
Calcification, focal			1 (2%)
#Brain	(50)	(8)	(50)
Abscess, NOS		1 (13%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Abscess, NOS			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Tarsal joint	(50)	(50)	(50)
Ankylosis	1 (2%)		
*Skeletal muscle	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Necrosis, NOS		1 (2%)	
Calcification, NOS		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
ALL OTHER SYSTEMS			
Omentum			
Necrosis, fat			1
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

		PAGE
TABLE B1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	101
TABLE B2	INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	104
TABLE B3	ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	110
TABLE B4a	HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	114
TABLE B4b	HISTORICAL INCIDENCE OF LARGE INTESTINE TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	114
TABLE B4c	HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	115
TABLE B4d	HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE	116
TABLE B5	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	117

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Squamous cell carcinoma	1 (2%)		1 (2%)
Basal cell carcinoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Basal cell tumor		1 (2%)	
Fibroma			1 (2%)
Lipoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	8 (16%)	9 (18%)	6 (12%)
#Liver	(50)	(50)	(50)
Leukemia, mononuclear cell	1 (2%)		
#Thymus	(43)	(44)	(39)
Squamous cell carcinoma		1 (2%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule	1 (2%)	3 (6%)	1 (2%)
#Pancreas	(48)	(50)	(50)
Acinar cell adenoma			1 (2%)
#Forestomach	(50)	(50)	(49)
Squamous cell carcinoma	1 (2%)		
#Jejunum	(50)	(50)	(50)
Leiomyoma			1 (2%)
#Colon	(46)	(50)	(47)
Adenocarcinoma, NOS			6 (13%)
Adenomatous polyp, NOS			7 (15%)
#Cecum	(46)	(50)	(47)
Lipoma	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	6 (12%)
Tubular cell adenocarcinoma			9 (18%)
#Urinary bladder	(50)	(50)	(46)
Transitional cell carcinoma		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary	(49)	(49)	(49)
Carcinoma, NOS	1 (2%)		
#Pituitary pars intermedia	(49)	(49)	(49)
Adenoma, NOS			1 (2%)
#Anterior pituitary	(49)	(49)	(49)
Carcinoma, NOS	3 (6%)	2 (4%)	1 (2%)
Adenoma, NOS	27 (55%)	18 (37%)	13 (27%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma		1 (2%)	1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	5 (10%)	1 (2%)	2 (4%)
#Thyroid	(47)	(49)	(50)
Follicular cell carcinoma	2 (4%)	1 (2%)	
C-cell adenoma			2 (4%)
C-cell carcinoma	2 (4%)		
#Pancreatic islets	(48)	(50)	(50)
Islet cell adenoma	1 (2%)		
Islet cell carcinoma	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
Fibroadenoma	20 (40%)	15 (30%)	1 (2%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	4 (8%)	2 (4%)	1 (2%)
Adenoma, NOS	1 (2%)	1 (2%)	
#Uterus	(49)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
Leiomyosarcoma		1 (2%)	
Endometrial stromal polyp	11 (22%)	13 (26%)	7 (14%)
Endometrial stromal sarcoma	1 (2%)		
#Ovary	(50)	(50)	(49)
Granulosa cell tumor		1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Granular cell tumor, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Sebaceous adenocarcinoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	6	4
Moribund sacrifice	9	17	5
Terminal sacrifice	34	27	41
TUMOR SUMMARY			
Total animals with primary tumors**	48	43	43
Total primary tumors	99	75	70
Total animals with benign tumors	44	34	30
Total benign tumors	69	53	44
Total animals with malignant tumors	24	18	22
Total malignant tumors	29	18	24
Total animals with tumors uncertain--benign or malignant	1	4	2
Total uncertain tumors	1	4	2

---

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: VEHICLE CONTROL

ANIMAL NUMBER	042	006	023	026	035	004	050	037	005	032	038	029	011	017	013	040	001	002	003	007	008	009	010	012	014
WEEKS ON STUDY	042	073	081	082	082	093	093	094	096	096	096	098	099	099	103	103	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Squamous cell carcinoma								X																	
Basal cell carcinoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Thymus	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+		+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule							X																		
Leukemia, mononuclear cell																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	−	−	−	−	+	+	−	+	+	+	+	+	−	−	−	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+
Lipoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS						X														X		X			
Adenoma, NOS			X	X					X					X	X	X		X			X		X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X				X						X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Follicular cell carcinoma																			X						
C-cell carcinoma																									
Parathyroid	+	−	−	+	+	+	−	−	−	+	−	−	+	−	+	+	+	−	−	−	−	+	−	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma											X														
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	+	+	+	N	N	+	N	+	N	+	+	+	+	+	+	+	N	N	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma					X	X				X		X		X		X	X	X	X						
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS															X	X									
Adenoma, NOS												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp		X										X									X				X
Endometrial stromal sarcoma																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X															
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N
Sebaceous adenocarcinoma																								X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell						X	X			X	X										X				

+	Tissue examined microscopically
−	Required tissue not examined microscopically
X	Tumor incidence
N	Necropsy, no autolysis, no microscopic examination
S	Animal missexed
	No tissue information submitted
C	Necropsy, no histology due to protocol
A	Autolysis
M	Animal missing
B	No necropsy performed

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL
(Continued)

ANIMAL NUMBER	015	016	018	019	020	021	022	023	024	025	027	028	030	031	034	038	039	041	043	044	045	046	047	048	049	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	104	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Squamous cell carcinoma																										1
Basal cell carcinoma					X																					1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Leukemia, mononuclear cell							X																			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	-	-	-	-	-	-	-	-	+	+	+	+	-	-	-	+	+	+	+	31
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma			X																							1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	48
Lipoma				X																						1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	49
Carcinoma, NOS												X														4
Adenoma, NOS	X	X	X	X			X		X	X			X		X	X	X	X		X	X		X	X		27
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma							X									X										5
Thyroid	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	47
Follicular cell carcinoma																					X					2
C-cell carcinoma						X		X																		2
Parathyroid	-	-	-	-	-	-	+	+	+	+	-	+	+	+	-	+	-	+	+	+	-	-	+	-	-	22
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																										1
Islet cell carcinoma	X														X											2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																					X					1
Fibroadenoma					X	X	X	X	X					X		X				X		X	X		X	20
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																		X			X					4
Adenoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp			X					X	X	X				X						X		X				11
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sebaceous adenocarcinoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell			X								X														X	6

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: LOW DOSE

ANIMAL NUMBER	032	040	027	014	017	035	050	005	008	001	015	003	031	039	046	033	016	021	004	013	029	019	041	002	006
WEEKS ON STUDY	033	058	069	070	071	075	079	080	080	081	082	086	086	094	095	097	098	099	101	101	103	103	103	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor																									X
Lipoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
Squamous cell carcinoma																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																	X				X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS														X			X								
Adenoma, NOS				X	X	X			X		X		X		X				X			X		X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
Parathyroid	+	-	-	+	-	-	-	-	+	+	-	-	-	-	-	+	-	+	-	-	+	-	-	-	-
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	+	N	N	+	N	+	N	N	+	+	+	N	+	N	+	+	+	+	+	+	+
Fibroadenoma								X		X				X							X	X			X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X						X																
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Leiomyosarcoma																									
Endometrial stromal polyp												X	X			X								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																						X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X													X	X		X		X	X		X		

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE
(Continued)

ANIMAL NUMBER	007	009	010	011	012	018	019	020	022	023	024	025	026	027	028	030	034	038	042	043	044	045	047	048	049	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor																										1
Lipoma								X																		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	44
Squamous cell carcinoma										X																1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule			X																							3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	-	-	-	-	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	39
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																		X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																		X								1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										2
Adenoma, NOS		X								X		X					X	X	X	X				X		18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																				X						1
Pheochromocytoma				X																						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma						X																				1
Parathyroid	-	-	-	-	+	+	+	-	-	+	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	14
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	N	N	+	N	*50
Fibroadenoma				X	X				X	X	X	X								X	X			X		15
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
Adenoma, NOS									X																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS		X																								1
Leiomyosarcoma																X										1
Endometrial stromal polyp	X		X	X	X			X		X								X		X			X			13
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell							X														X					9

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: HIGH DOSE

ANIMAL NUMBER	021	035	043	032	044	048	006	034	023	001	002	003	004	005	007	008	009	010	011	012	013	014	015	016	017
WEEKS ON STUDY	033	049	072	088	088	094	096	097	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	[illegible]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																		X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Acinar cell adenoma													X												
Esophagus	+	+	−	−	−	−	+	+	+	−	−	−	−	+	+	−	+	+	+	+	+	+	−	−	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																						X			
Large intestine	−	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X		X					
Adenomatous polyp, NOS				X													X	X	X						
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma													X			X					X			X	
Tubular cell adenocarcinoma									X					X				X				X			
Urinary bladder	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS			X											X	X	X	X		X						
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma											X														
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma															X										X
Parathyroid	−	−	−	−	−	−	+	−	−	+	+	+	+	+	+	−	+	−	−	+	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	+	N	N	N	+	N	N	+	+	+	+	N	N	+	+	+	+	+	N
Fibroadenoma																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp					X			X				X					X	X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X				X				X	X	X													

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE
(Continued)

ANIMAL NUMBER	018	019	020	022	024	025	026	027	028	029	030	031	033	036	037	038	039	040	041	042	045	046	047	049	050	
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	-	+	+	+	+	+	-	+	-	-	+	+	-	+	+	+	+	+	+	+	-	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																										1
Esophagus	-	-	-	-	+	-	+	+	+	-	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	23
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma, NOS			X		X																			X	X	6
Adenomatous polyp, NOS							X		X										X							7
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma														X		X										6
Tubular cell adenocarcinoma			X				X										X				X	X				9
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																							X			1
Adenoma, NOS			X				X				X		X	X	X					X		X				14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma						X																				1
Pheochromocytoma																				X						2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma																										2
Parathyroid	+	-	+	-	-	-	-	-	-	+	-	-	+	-	-	+	+	-	-	+	+	+	+	+	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	N	+	N	N	+	N	N	+	N	+	N	+	N	+	N	N	N	N	+	+	N	N	*50
Fibroadenoma			X																							1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp					X														X							7
Ovary	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell												X														6

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	9/50 (18%)	9/50 (18%)	6/50 (12%)
Adjusted Rates (b)	22.4%	24.9%	13.6%
Terminal Rates (c)	5/34 (15%)	2/27 (7%)	4/41 (10%)
Week of First Observation	93	56	49
Life Table Tests (d)	P=0.190N	P=0.440	P=0.218N
Incidental Tumor Tests (d)	P=0.450N	P=0.550	P=0.403N
Cochran-Armitage Trend Test (d)	P=0.248N		
Fisher Exact Test (d)		P=0.603N	P=0.288N
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	2.2%	9.7%	2.4%
Terminal Rates (c)	0/34 (0%)	1/27 (4%)	1/41 (2%)
Week of First Observation		98	104
Life Table Tests (d)	P=0.559N	P=0.245	P=0.740N
Incidental Tumor Tests (d)	P=0.452	P=0.256	P=0.681
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753N
Large Intestine: Adenomatous Polyp			
Overall Rates (a)	0/46 (0%)	0/50 (0%)	7/47 (15%)
Adjusted Rates (b)	0.0%	0.0%	16.8%
Terminal Rates (c)	0/32 (0%)	0/27 (0%)	6/40 (15%)
Week of First Observation			88
Life Table Tests (d)	P=0.003	(e)	P=0.018
Incidental Tumor Tests (d)	P=0.002	(e)	P=0.010
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		(e)	P=0.007
Large Intestine: Adenocarcinoma			
Overall Rates (a)	0/46 (0%)	0/50 (0%)	6/47 (13%)
Adjusted Rates (b)	0.0%	0.0%	15.0%
Terminal Rates (c)	0/32 (0%)	0/27 (0%)	6/40 (15%)
Week of First Observation			104
Life Table Tests (d)	P=0.007	(e)	P=0.032
Incidental Tumor Tests (d)	P=0.007	(e)	P=0.032
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		(e)	P=0.014
Large Intestine: Adenomatous Polyp or Adenocarcinoma			
Overall Rates (a)	0/46 (0%)	0/50 (0%)	12/47 (26%)
Adjusted Rates (b)	0.0%	0.0%	29.1%
Terminal Rates (c)	0/32 (0%)	0/27 (0%)	11/40 (28%)
Week of First Observation			88
Life Table Tests (d)	P<0.001	(e)	P=0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		(e)	P<0.001
Kidney: Tubular Cell Adenoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	0.0%	3.7%	14.6%
Terminal Rates (c)	0/34 (0%)	1/27 (4%)	6/41 (15%)
Week of First Observation		105	104
Life Table Tests (d)	P=0.011	P=0.454	P=0.030
Incidental Tumor Tests (d)	P=0.011	P=0.454	P=0.030
Cochran-Armitage Trend Test (d)	P=0.005		
Fisher Exact Test (d)		P=0.500	P=0.013

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Kidney: Tubular Cell Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	9/50 (18%)
Adjusted Rates (b)	0.0%	0.0%	21.4%
Terminal Rates (c)	0/34 (0%)	0/27 (0%)	8/41 (20%)
Week of First Observation			103
Life Table Tests (d)	P<0.001	(e)	P=0.006
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.003
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		(e)	P=0.001
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	15/50 (30%)
Adjusted Rates (b)	0.0%	3.7%	35.7%
Terminal Rates (c)	0/34 (0%)	1/27 (4%)	14/41 (34%)
Week of First Observation		105	103
Life Table Tests (d)	P<0.001	P=0.454	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.454	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.500	P<0.001
Pituitary Gland: Adenoma			
Overall Rates (a)	27/49 (55%)	18/49 (37%)	13/49 (27%)
Adjusted Rates (b)	67.1%	47.3%	30.7%
Terminal Rates (c)	21/34 (62%)	9/27 (33%)	12/41 (29%)
Week of First Observation	81	70	72
Life Table Tests (d)	P=0.001N	P=0.259N	P<0.001N
Incidental Tumor Tests (d)	P=0.002N	P=0.044N	P=0.002N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.052N	P=0.004N
Pituitary Gland: Carcinoma			
Overall Rates (a)	4/49 (8%)	2/49 (4%)	1/49 (2%)
Adjusted Rates (b)	10.8%	5.6%	2.4%
Terminal Rates (c)	3/34 (9%)	0/27 (0%)	1/41 (2%)
Week of First Observation	93	94	104
Life Table Tests (d)	P=0.103N	P=0.432N	P=0.139N
Incidental Tumor Tests (d)	P=0.180N	P=0.390N	P=0.194N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test (d)		P=0.339N	P=0.181N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	31/49 (63%)	20/49 (41%)	14/49 (29%)
Adjusted Rates (b)	75.3%	50.2%	33.1%
Terminal Rates (c)	24/34 (71%)	9/27 (33%)	13/41 (32%)
Week of First Observation	81	70	72
Life Table Tests (d)	P<0.001N	P=0.194N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.021N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.021N	P<0.001N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	2/49 (4%)
Adjusted Rates (b)	14.1%	3.7%	4.9%
Terminal Rates (c)	4/34 (12%)	1/27 (4%)	2/41 (5%)
Week of First Observation	99	105	104
Life Table Tests (d)	P=0.100N	P=0.160N	P=0.154N
Incidental Tumor Tests (d)	P=0.125N	P=0.157N	P=0.213N
Cochran-Armitage Trend Test (d)	P=0.138N		
Fisher Exact Test (d)		P=0.102N	P=0.226N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	3/48 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.2%	0.0%	0.0%
Terminal Rates (c)	2/34 (6%)	0/27 (0%)	0/41 (0%)
Week of First Observation	96		
Life Table Tests (d)	P=0.035N	P=0.162N	P=0.098N
Incidental Tumor Tests (d)	P=0.042N	P=0.144N	P=0.141N
Cochran-Armitage Trend Test (d)	P=0.034N		
Fisher Exact Test (d)		P=0.114N	P=0.114N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	20/50 (40%)	15/50 (30%)	1/50 (2%)
Adjusted Rates (b)	49.3%	45.5%	2.4%
Terminal Rates (c)	14/34 (41%)	10/27 (37%)	1/41 (2%)
Week of First Observation	82	80	104
Life Table Tests (d)	P<0.001N	P=0.472N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.345N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.201N	P<0.001N
Clitoral Gland: Carcinoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	11.1%	4.4%	2.4%
Terminal Rates (c)	2/34 (6%)	0/27 (0%)	1/41 (2%)
Week of First Observation	103	69	104
Life Table Tests (d)	P=0.103N	P=0.415N	P=0.135N
Incidental Tumor Tests (d)	P=0.147N	P=0.225N	P=0.259N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test (d)		P=0.339N	P=0.181N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	13.4%	7.9%	2.4%
Terminal Rates (c)	2/34 (6%)	1/27 (4%)	1/41 (2%)
Week of First Observation	98	69	104
Life Table Tests (d)	P=0.061N	P=0.452N	P=0.076N
Incidental Tumor Tests (d)	P=0.101N	P=0.277N	P=0.198N
Cochran-Armitage Trend Test (d)	P=0.070N		
Fisher Exact Test (d)		P=0.357N	P=0.102N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	11/49 (22%)	13/50 (26%)	7/50 (14%)
Adjusted Rates (b)	30.6%	42.0%	16.1%
Terminal Rates (c)	9/33 (27%)	10/27 (37%)	5/41 (12%)
Week of First Observation	73	88	88
Life Table Tests (d)	P=0.098N	P=0.225	P=0.120N
Incidental Tumor Tests (d)	P=0.143N	P=0.348	P=0.190N
Cochran-Armitage Trend Test (d)	P=0.179N		
Fisher Exact Test (d)		P=0.430	P=0.204N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	12/49 (24%)	13/50 (26%)	7/50 (14%)
Adjusted Rates (b)	33.5%	42.0%	16.1%
Terminal Rates (c)	10/33 (30%)	10/27 (37%)	5/41 (12%)
Week of First Observation	73	88	88
Life Table Tests (d)	P=0.063N	P=0.295	P=0.077N
Incidental Tumor Tests (d)	P=0.094N	P=0.432	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.124N		
Fisher Exact Test (d)		P=0.523	P=0.142N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site

(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality

(c) Observed tumor incidence at terminal kill

(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

(e) No P value is reported because no tumors were observed in the 50 mg/kg and vehicle control groups.

TABLE B4a. HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Historical Incidence at EG&G Mason Research Institute

No tubular cell tumors have been observed in 250 vehicle control animals

Overall Historical Incidence	No. Examined	No. of Tumors	Diagnosis
		1	Adenoma, NOS
		1	Tubular cell adenoma
	1,447	2 (0.1%)	

(a) Data as of August 30, 1985, for studies of at least 104 weeks. No more than one tumor has been observed in any vehicle control group.

TABLE B4b. HISTORICAL INCIDENCE OF LARGE INTESTINE TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Historical Incidence at EG&G Mason Research Institute

No large intestine tumors have been observed in 236 corn oil vehicle control animals.

Overall Historical Incidence

No large intestine tumors have been observed in 1,400 corn oil vehicle control animals.

(a) Data as of August 30, 1985, for studies of at least 104 weeks.

TABLE B4c. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls Fibroadenoma	All Adenomas
Historical Incidence at EG&G Mason Research Institute		
Diglycidyl resorcinol ether	18/50	18/50
Diglycidyl resorcinol ether	17/50	17/50
1,2-Dichloropropane	15/50	15/50
Chlorodibromomethane	18/50	18/50
n-Butyl chloride	16/50	16/50
TOTAL	84/250 (33.6%)	84/250 (33.6%)
SD (b)	2.61%	2.61%
Range (c)		
High	18/50	18/50
Low	15/50	15/50
Overall Historical Incidence		
TOTAL	365/1,450 (25.2%)	(d) 382/1,450 (26.3%)
SD (b)	7.51%	7.67%
Range (c)		
High	19/50	19/50
Low	6/50	7/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks

(b) Standard deviation

(c) Range and SD are presented for groups of 35 or more animals.

(d) Includes 10 adenomas, NOS; 1 papillary adenoma; 4 cystadenomas, NOS; and 1 papillary cystadenoma

TABLE B4d. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
Study	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	18/50	1/50	19/50
Diglycidyl resorcinol ether	16/50	2/50	17/50
1,2-Dichloropropane	16/49	3/49	19/49
Chlorodibromomethane	11/47	5/47	16/47
n-Butyl chloride	22/49	2/49	24/49
TOTAL	83/245 (33.9%)	13/245 (5.3%)	95/245 (38.8%)
SD (b)	7.76%	3.29%	6.12%
Range (c)			
High	22/49	5/47	24/49
Low	11/47	1/50	17/50
Overall Historical Incidence			
TOTAL	520/1,407 (37.0%)	43/1,407 (3.1%)	561/1,407 (39.9%)
SD (b)	8.35%	2.90%	8.47%
Range (c)			
High	27/49	5/47	30/49
Low	9/50	0/50	11/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks

(b) Standard deviation

(c) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, acute		† 1 (2%)	
Hyperkeratosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Abscess, NOS			1 (2%)
Inflammation, chronic		1 (2%)	
RESPIRATORY SYSTEM			
#Trachea	(49)	(50)	(49)
Inflammation, chronic focal	1 (2%)		
#Peritracheal tissue	(49)	(50)	(49)
Inflammation, chronic		1 (2%)	
#Lung	(50)	(50)	(50)
Inflammation, interstitial	2 (4%)		2 (4%)
Bronchopneumonia, acute		1 (2%)	1 (2%)
Pneumonia, interstitial chronic	1 (2%)		3 (6%)
Granuloma, NOS			1 (2%)
Hyperplasia, alveolar epithelium	2 (4%)		
#Lung/alveoli	(50)	(50)	(50)
Hemorrhage	2 (4%)		
HEMATOPOIETIC SYSTEM			
#Spleen	(50)	(50)	(50)
Hemosiderosis	2 (4%)	3 (6%)	2 (4%)
Hematopoiesis	1 (2%)	1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Inflammation, chronic focal			2 (4%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	10 (20%)	9 (18%)	10 (20%)
*Mesenteric artery	(50)	(50)	(50)
Thrombus, organized	1 (2%)		
Inflammation, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Inflammation, acute		2 (4%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal			2 (4%)
Calcification, focal			1 (2%)
Hyperplasia, focal	1 (2%)		
Metaplasia, squamous		2 (4%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(50)	(50)
Congenital malformation, NOS	1 (2%)		2 (4%)
Inflammation, chronic focal	3 (6%)	2 (4%)	4 (8%)
Inflammation granulomatous focal	1 (2%)		
Cholangiofibrosis			5 (10%)
Degeneration, NOS	1 (2%)		
Necrosis, focal			1 (2%)
Necrosis, hemorrhagic		1 (2%)	
Metamorphosis, fatty	7 (14%)	22 (44%)	13 (26%)
Hemosiderosis	1 (2%)		
Mitotic alteration		1 (2%)	1 (2%)
Cytoplasmic vacuolization	1 (2%)		
Basophilic cyto change	40 (80%)	20 (40%)	29 (58%)
Ground glass cyto change		1 (2%)	2 (4%)
Focal cellular change	4 (8%)	4 (8%)	11 (22%)
Eosinophilic cyto change		1 (2%)	11 (22%)
Clear cell change	4 (8%)	6 (12%)	39 (78%)
Atypia, NOS			1 (2%)
Hyperplasia, focal		1 (2%)	
Angiectasis	3 (6%)	3 (6%)	
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, NOS	1 (2%)	2 (4%)	
#Bile duct	(50)	(50)	(50)
Multiple cysts			2 (4%)
Inflammation, chronic	2 (4%)		
Hyperplasia, NOS	29 (58%)	15 (30%)	15 (30%)
#Pancreas	(48)	(50)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic focal		1 (2%)	
Necrosis, NOS		1 (2%)	
Hyperplastic nodule		1 (2%)	
#Pancreatic acinus	(48)	(50)	(50)
Atrophy, NOS		1 (2%)	
Atrophy, focal	5 (10%)	8 (16%)	2 (4%)
Hyperplasia, focal			1 (2%)
#Pancreas/interstitial tissue	(48)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Gastric submucosa	(50)	(50)	(49)
Edema, NOS		1 (2%)	
#Forestomach	(50)	(50)	(49)
Ulcer, NOS		1 (2%)	1 (2%)
Inflammation, acute		3 (6%)	1 (2%)
Hyperkeratosis		1 (2%)	1 (2%)
Acanthosis		1 (2%)	1 (2%)
#Colon	(46)	(50)	(47)
Parasitism	5 (11%)	4 (8%)	3 (6%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Multiple cysts		1 (2%)	
Inflammation, chronic focal	1 (2%)	1 (2%)	
Nephrosis, NOS	26 (52%)	17 (34%)	41 (82%)
#Kidney/interstitium	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Kidney/tubule	(50)	(50)	(50)
Necrosis, focal	2 (4%)		
Pigmentation, NOS		1 (2%)	
Hyperplasia, tubular cell		1 (2%)	4 (8%)
#Urinary bladder	(50)	(50)	(46)
Hyperplasia, epithelial	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(49)	(49)	(49)
Cyst, NOS	2 (4%)		
Multiple cysts	2 (4%)	1 (2%)	
Hyperplasia, focal	1 (2%)		
#Anterior pituitary	(49)	(49)	(49)
Multiple cysts	3 (6%)	4 (8%)	
Cytoplasmic vacuolization		1 (2%)	
Hypertrophy, focal		1 (2%)	1 (2%)
Hyperplasia, focal	3 (6%)	11 (22%)	8 (16%)
Angiectasis	3 (6%)		2 (4%)
#Adrenal	(50)	(50)	(49)
Amyloidosis			1 (2%)
#Adrenal cortex	(50)	(50)	(49)
Degeneration, NOS	10 (20%)	10 (20%)	4 (8%)
Metamorphosis, fatty	1 (2%)		
Hyperplastic nodule		1 (2%)	1 (2%)
Hyperplasia, focal		3 (6%)	3 (6%)
Angiectasis	1 (2%)		
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Thyroid	(47)	(49)	(50)
Cystic follicles		1 (2%)	2 (4%)
Hyperplasia, C-cell	4 (9%)	4 (8%)	5 (10%)
Hyperplasia, follicular cell		1 (2%)	
#Thyroid follicle	(47)	(49)	(50)
Hyperplasia, cystic		1 (2%)	
#Pancreatic islets	(48)	(50)	(50)
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, cystic	18 (36%)	12 (24%)	2 (4%)
*Clitoral gland	(50)	(50)	(50)
Retention of content		2 (4%)	
Inflammation, suppurative	1 (2%)		
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, chronic	2 (4%)		
Hyperplasia, NOS	2 (4%)	1 (2%)	1 (2%)
*Vagina	(50)	(50)	(50)
Hemorrhage	1 (2%)		
#Uterus	(49)	(50)	(50)
Inflammation, suppurative		2 (4%)	
Hyperplasia, adenomatous		1 (2%)	
#Cervix uteri	(49)	(50)	(50)
Fibrosis		1 (2%)	
#Uterus/endometrium	(49)	(50)	(50)
Cyst, NOS			2 (4%)
Hyperplasia, cystic	5 (10%)	4 (8%)	
#Fallopian tube	(49)	(50)	(50)
Retention fluid	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Ovary/parovarian	(50)	(50)	(49)
Necrosis, fat		1 (2%)	1 (2%)
#Ovary	(50)	(50)	(49)
Cyst, NOS	2 (4%)	3 (6%)	2 (4%)
Multiple cysts	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Steatitis	1 (2%)		
Necrosis, fat	5 (10%)	5 (10%)	1 (2%)
ALL OTHER SYSTEMS			
Foot			
Ulcer, NOS	1		
Inflammation, acute	1		
Adipose tissue			
Necrosis, NOS		1	
Omentum			
Necrosis, fat	3		
SPECIAL MORPHOLOGY SUMMARY			
None			

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* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.

† Multiple occurrence of morphology in the same organ. Tissue counted once only.

# Number of animals examined microscopically at this site

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

		PAGE
TABLE C1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	123
TABLE C2	INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	126
TABLE C3	ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	132
TABLE C4	HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE	136
TABLE C5	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	137

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Basal cell carcinoma		1 (2%)	
Keratoacanthoma			1 (2%)
*Subcutaneous tissue	(49)	(50)	(50)
Fibroma		3 (6%)	1 (2%)
Fibrosarcoma	7 (14%)	5 (10%)	3 (6%)
Neurofibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(50)
Hepatocellular carcinoma, metastatic	2 (4%)	2 (4%)	1 (2%)
Alveolar/bronchiolar adenoma	8 (16%)	1 (2%)	6 (12%)
Alveolar/bronchiolar carcinoma	4 (8%)	2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Malignant lymphoma, NOS		1 (2%)	
Malignant lymphoma, lymphocytic type		5 (10%)	3 (6%)
Malignant lymphoma, histiocytic type	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, mixed type	4 (8%)	2 (4%)	4 (8%)
#Jejunum	(49)	(50)	(50)
Malignant lymphoma, histiocytic type	1 (2%)		
CIRCULATORY SYSTEM			
*Abdominal cavity	(49)	(50)	(50)
Hemangiosarcoma		1 (2%)	
*Sup. pancreaticoduodenal artery	(49)	(50)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	
#Liver	(49)	(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Hepatocellular adenoma	10 (20%)	4 (8%)	12 (24%)
Hepatocellular carcinoma	8 (16%)	12 (24%)	11 (22%)
#Stomach	(49)	(50)	(49)
Adenocarcinoma, NOS		1 (2%)	
#Forestomach	(49)	(50)	(49)
Squamous cell papilloma		1 (2%)	
*Rectum	(49)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Tubular cell adenoma	1 (2%)	2 (4%)	6 (12%)
Tubular cell adenocarcinoma			4 (8%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(45)	(48)
Adenoma, NOS	1 (2%)		1 (2%)
#Adrenal	(48)	(46)	(46)
Cortical adenoma	1 (2%)		
#Adrenal/capsule	(48)	(46)	(46)
Adenoma, NOS		1 (2%)	2 (4%)
#Adrenal medulla	(48)	(46)	(46)
Pheochromocytoma	3 (6%)	1 (2%)	1 (2%)
Ganglioneuroma		1 (2%)	
#Thyroid	(48)	(44)	(49)
Follicular cell adenoma	2 (4%)		
C-cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
#Testis	(49)	(50)	(50)
Interstitial cell tumor		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Brain	(49)	(50)	(50)
Medulloblastoma		1 (2%)	
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(50)	(50)
Adenoma, NOS	3 (6%)	3 (6%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	12	6
Moribund sacrifice	6	7	2
Terminal sacrifice	34	31	42
Dosing accident	2		
Animal missing	1		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	38	36	35
Total primary tumors	59	50	60
Total animals with benign tumors	23	16	24
Total benign tumors	30	18	32
Total animals with malignant tumors	25	26	23
Total malignant tumors	29	32	28
Total animals with secondary tumors##	3	2	1
Total secondary tumors	3	3	1

---

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
## Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: VEHICLE CONTROL

ANIMAL NUMBER	004	008	026	029	039	001	021	037	003	033	032	030	044	027	042	034	002	005	006	007	009	010	011	012	013
WEEKS ON STUDY	000	000	009	076	079	080	082	082	085	089	090	093	094	096	101	103	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	M	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	-	+	+	+	+
Fibrosarcoma								X		X									X						
Neurofibrosarcoma														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																							X		
Alveolar/bronchiolar adenoma						X	X	X							X			X							
Alveolar/bronchiolar carcinoma											X														
Trachea	+	+	+	+	M	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	M	+	-	+	+	-	+	-	+	+	+	+	-	+	+	+	+	+	+	-	+
Thymus	-	+	-	-	M	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	-	+	-	+	-
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X			X					
Hepatocellular carcinoma							X				X					X							X		
Hemangioma													X												
Hemangiosarcoma						X																			
Bile duct	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	M	-	N	+	N	+	N	N	+	+	-	+	+	+	+	N	+	+	N	+	+
Pancreas	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																						X			
Large intestine	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Rectum	N	N	N	N	M	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS									X																
URINARY SYSTEM																									
Kidney	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma												X						X							
Thyroid	+	+	+	+	M	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																			X						
C-cell carcinoma																									
Parathyroid	-	-	-	+	M	-	-	-	+	+	-	-	-	-	+	+	-	+	-	+	+	-	-	-	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
Testis	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	M	-	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									X
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma metastatic											X														
Malignant lymphoma, histiocytic type																									X
Malignant lymphoma, mixed type																								X	

+	Tissue examined microscopically
-	Required tissue not examined microscopically
X	Tumor incidence
N	Necropsy, no autolysis, no microscopic examination
S	Animal missexed
	No tissue information submitted
C:	Necropsy, no histology due to protocol
A:	Autolysis
M:	Animal missing
B:	No necropsy performed

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	014	015	016	017	018	019	020	022	023	024	025	028	035	036	041	043	045	049	031	038	040	046	047	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma		X				X													X		X					7
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic	X																									2
Alveolar/bronchiolar adenoma										X						X					X					8
Alveolar/bronchiolar carcinoma					X	X																	X			4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	−	+	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma			X	X				X		X						X				X	X	X				10
Hepatocellular carcinoma	X					X			X	X																8
Hemangioma																										1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	−	43
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, histiocytic type																										1
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	45
Rectum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenocarcinoma, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma							X																			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Adenoma, NOS														X												1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Cortical adenoma												X														1
Pheochromocytoma																					X					3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma						X																				2
C-cell carcinoma																					X					1
Parathyroid	+	+	+	+	+	−	+	+	−	−	+	−	−	+	+	+	−	+	+	+	+	+	−	−	+	26
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS				X																		X				3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Alveolar/bronchiolar carcinoma, metas																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type			X										X	X												4

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: LOW DOSE

ANIMAL NUMBER	002	043	001	045	003	004	005	031	050	026	049	018	023	021	046	047	017	025	006	007	008	009	010	011	012
WEEKS ON STUDY	001	061	063	063	072	072	072	073	081	082	085	088	088	094	098	098	102	103	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								X	
Fibrosarcoma										X	X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic												X													
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																							X		
Trachea	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	-	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Lymph nodes	+	+	+	-	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	-	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	+	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic												X													
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma								X	X			X	X	X				X		X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	N	+	N	+	+	+	N	+	+	N	+	N	+	N	+	N	+	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Esophagus	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Adenocarcinoma, NOS																			X						
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	-	-	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+
Adrenal	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+
Adenoma, NOS															X										
Pheochromocytoma																									
Ganglioneuroma									X																
Thyroid	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Parathyroid	-	-	-	-	+	-	+	+	+	+	-	+	+	-	-	-	+	-	-	+	+	+	-	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+
Interstitial cell tumor																									
Prostate	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Medulloblastoma		X																							
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																		X							
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma															X										
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS			X																						
Malignant lymphoma, lymphocytic type																X									
Malignant lymphoma, histiocytic type												X													
Malignant lymphoma, mixed type																				X					

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE
(Continued)

ANIMAL NUMBER	013	014	015	018	019	020	021	024	027	028	029	030	032	033	034	035	036	037	038	039	040	041	042	044	048	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Basal cell carcinoma																	X									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Fibroma		X															X									3
Fibrosarcoma								X		X	X															5
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic														X												2
Alveolar/bronchiolar adenoma																					X					1
Alveolar/bronchiolar carcinoma	X																									2
Trachea	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	45
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	-	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X			X	X			X				4
Hepatocellular carcinoma	X		X							X				X		X										12
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	N	N	N	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47
Esophagus	+	-	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-	+	-	+	+	+	+	+	+	34
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																		X								1
Adenocarcinoma, NOS																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma			X	X																						2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adrenal	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS																										1
Pheochromocytoma											X															1
Ganglioneuroma																										1
Thyroid	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	44
Parathyroid	+	-	-	+	+	-	+	+	+	-	+	+	+	-	-	+	-	+	-	-	+	+	-	+	+	28
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor				X																						1
Prostate	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Medulloblastoma																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS												X	X													3
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Malignant lymphoma, lymphocytic type							X	X									X								X	5
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																				X						2

* Animals necropsied

TABLE C3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: HIGH DOSE

ANIMAL NUMBER	027	030	031	013	028	045	034	017	001	002	003	004	005	006	007	008	009	010	011	012	014	015	016	018	019
WEEKS ON STUDY	015	015	016	026	078	091	094	099	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma									X																
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																						X			
Alveolar/bronchiolar adenoma											X						X	X							
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Lymph nodes	+	+	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	-	-	+	+	+	+
Thymus	-	+	-	-	-	-	-	-	+	+	+	-	-	+	+	+	+	-	+	+	-	-	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X	X										X			X		X	
Hepatocellular carcinoma					X	X	X		X				X	X					X			X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	N	N	N	N	+	+	+	+	N	+	+	N	+	+	+	N	N	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	-	-	-	-	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																X									
Tubular cell adenocarcinoma																		X					X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Adenoma, NOS																				X					
Pheochromocytoma																							X		
Thyroid	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	-	-	+	-	+	-	-	-	-	+	+	+	-	-	-	-	+	-	-	-	+	+	+	-	-
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor										X															
Prostate	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type									X												X				
Malignant lymphoma, histiocytic type								X																	
Malignant lymphoma, mixed type														X											

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	020	021	022	023	024	025	026	029	032	033	035	036	037	038	039	040	041	042	043	044	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Keratoacanthoma	X																									1
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Fibroma	X																									1
Fibrosarcoma				X							X															3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma							X		X						X											6
Alveolar/bronchiolar carcinoma				X			X																			2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	-	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X			X													X			X	X	X		X	12
Hepatocellular carcinoma						X						X		X												11
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	N	N	N	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	+	+	37
Stomach	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	-	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma	X				X						X										X				X	6
Tubular cell adenocarcinoma		X																							X	4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																		X								1
Adrenal	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	48
Adenoma, NOS							X																			2
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	+	+	+	+	+	-	+	+	+	+	-	+	-	-	+	-	-	+	+	-	+	-	-	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type					X																					3
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type							X										X						X			4

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	25 mg/kg	50 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	9.4%	2.4%
Terminal Rates (c)	0/34 (0%)	3/32 (9%)	1/42 (2%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.451	P=0.110	P=0.542
Incidental Tumor Tests (d)	P=0.451	P=0.110	P=0.542
Cochran-Armitage Trend Test (d)	P=0.384		
Fisher Exact Test (d)		P=0.125	P=0.505
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	7/49 (14%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	18.7%	13.8%	7.1%
Terminal Rates (c)	5/34 (15%)	3/32 (9%)	3/42 (7%)
Week of First Observation	82	82	104
Life Table Tests (d)	P=0.080N	P=0.427N	P=0.099N
Incidental Tumor Tests (d)	P=0.177N	P=0.450N	P=0.197N
Cochran-Armitage Trend Test (d)	P=0.115N		
Fisher Exact Test (d)		P=0.365N	P=0.151N
Subcutaneous Tissue: Fibrosarcoma or Neurofibrosarcoma			
Overall Rates (a)	8/49 (16%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	20.9%	13.8%	7.1%
Terminal Rates (c)	5/34 (15%)	3/32 (9%)	3/42 (7%)
Week of First Observation	82	82	104
Life Table Tests (d)	P=0.046N	P=0.323N	P=0.059N
Incidental Tumor Tests (d)	P=0.124N	P=0.336N	P=0.157N
Cochran-Armitage Trend Test (d)	P=0.067N		
Fisher Exact Test (d)		P=0.264N	P=0.094N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	7/49 (14%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	18.7%	22.7%	9.5%
Terminal Rates (c)	5/34 (15%)	6/32 (19%)	4/42 (10%)
Week of First Observation	82	82	104
Life Table Tests (d)	P=0.142N	P=0.448	P=0.170N
Incidental Tumor Tests (d)	P=0.272N	P=0.421	P=0.304N
Cochran-Armitage Trend Test (d)	P=0.214N		
Fisher Exact Test (d)		P=0.517	P=0.251N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	8/49 (16%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	20.9%	22.7%	9.5%
Terminal Rates (c)	5/34 (15%)	6/32 (19%)	4/42 (10%)
Week of First Observation	82	82	104
Life Table Tests (d)	P=0.091N	P=0.553	P=0.109N
Incidental Tumor Tests (d)	P=0.206N	P=0.533	P=0.250N
Cochran-Armitage Trend Test (d)	P=0.142N		
Fisher Exact Test (d)		P=0.590N	P=0.168N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	8/49 (16%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	19.9%	3.1%	14.3%
Terminal Rates (c)	4/34 (12%)	1/32 (3%)	6/42 (14%)
Week of First Observation	80	104	104
Life Table Tests (d)	P=0.222N	P=0.026N	P=0.273N
Incidental Tumor Tests (d)	P=0.390N	P=0.025N	P=0.564N
Cochran-Armitage Trend Test (d)	P=0.296N		
Fisher Exact Test (d)		P=0.014N	P=0.371N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	4/49 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	11.1%	6.2%	4.8%
Terminal Rates (c)	3/34 (9%)	2/32 (6%)	2/42 (5%)
Week of First Observation	90	104	104
Life Table Tests (d)	P=0.186N	P=0.367N	P=0.253N
Incidental Tumor Tests (d)	P=0.237N	P=0.375N	P=0.361N
Cochran-Armitage Trend Test (d)	P=0.244N		
Fisher Exact Test (d)		P=0.329N	P=0.329N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	12/49 (24%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	29.7%	9.4%	16.7%
Terminal Rates (c)	7/34 (21%)	3/32 (9%)	7/42 (17%)
Week of First Observation	80	104	104
Life Table Tests (d)	P=0.055N	P=0.021N	P=0.082N
Incidental Tumor Tests (d)	P=0.132N	P=0.019N	P=0.274N
Cochran-Armitage Trend Test (d)	P=0.094N		
Fisher Exact Test (d)		P=0.010N	P=0.142N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	0/49 (0%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	0.0%	14.9%	7.1%
Terminal Rates (c)	0/34 (0%)	4/32 (13%)	3/42 (7%)
Week of First Observation		98	104
Life Table Tests (d)	P=0.202	P=0.030	P=0.161
Incidental Tumor Tests (d)	P=0.162	P=0.030	P=0.161
Cochran-Armitage Trend Test (d)	P=0.138		
Fisher Exact Test (d)		P=0.030	P=0.125
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/49 (8%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	11.8%	6.2%	9.5%
Terminal Rates (c)	4/34 (12%)	2/32 (6%)	4/42 (10%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.462N	P=0.364N	P=0.524N
Incidental Tumor Tests (d)	P=0.462N	P=0.364N	P=0.524N
Cochran-Armitage Trend Test (d)	P=0.569N		
Fisher Exact Test (d)		P=0.329N	P=0.631N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	6/49 (12%)	9/50 (18%)	8/50 (16%)
Adjusted Rates (b)	17.6%	24.6%	18.6%
Terminal Rates (c)	6/34 (18%)	6/32 (19%)	7/42 (17%)
Week of First Observation	104	63	99
Life Table Tests (d)	P=0.506	P=0.254	P=0.553
Incidental Tumor Tests (d)	P=0.388	P=0.314	P=0.493
Cochran-Armitage Trend Test (d)	P=0.354		
Fisher Exact Test (d)		P=0.303	P=0.403
Liver: Hepatocellular Adenoma			
Overall Rates (a)	10/49 (20%)	4/50 (8%)	12/50 (24%)
Adjusted Rates (b)	29.4%	12.5%	27.9%
Terminal Rates (c)	10/34 (29%)	4/32 (13%)	11/42 (26%)
Week of First Observation	104	104	99
Life Table Tests (d)	P=0.544	P=0.086N	P=0.569N
Incidental Tumor Tests (d)	P=0.511	P=0.086N	P=0.577
Cochran-Armitage Trend Test (d)	P=0.363		
Fisher Exact Test (d)		P=0.068N	P=0.426

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	8/49 (16%)	12/50 (24%)	11/50 (22%)
Adjusted Rates (b)	21.1%	30.7%	24.3%
Terminal Rates (c)	5/34 (15%)	6/32 (19%)	8/42 (19%)
Week of First Observation	82	73	78
Life Table Tests (d)	P=0.436	P=0.200	P=0.468
Incidental Tumor Tests (d)	P=0.112	P=0.217	P=0.167
Cochran-Armitage Trend Test (d)	P=0.285		
Fisher Exact Test (d)		P=0.242	P=0.323
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	17/49 (35%)	16/50 (32%)	20/50 (40%)
Adjusted Rates (b)	45.6%	41.3%	43.5%
Terminal Rates (c)	14/34 (41%)	10/32 (31%)	16/42 (38%)
Week of First Observation	82	73	78
Life Table Tests (d)	P=0.507N	P=0.579N	P=0.536N
Incidental Tumor Tests (d)	P=0.237	P=0.537N	P=0.313
Cochran-Armitage Trend Test (d)	P=0.326		
Fisher Exact Test (d)		P=0.472N	P=0.368
Kidney: Tubular Cell Adenoma			
Overall Rates (a)	1/49 (2%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (b)	2.9%	6.3%	14.3%
Terminal Rates (c)	1/34 (3%)	2/32 (6%)	6/42 (14%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.056	P=0.479	P=0.098
Incidental Tumor Tests (d)	P=0.056	P=0.479	P=0.098
Cochran-Armitage Trend Test (d)	P=0.031		
Fisher Exact Test (d)		P=0.508	P=0.059
Kidney: Tubular Cell Adenocarcinoma			
Overall Rates (a)	0/49 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	9.5%
Terminal Rates (c)	0/34 (0%)	0/32 (0%)	4/42 (10%)
Week of First Observation			104
Life Table Tests (d)	P=0.026	(e)	P=0.093
Incidental Tumor Tests (d)	P=0.026	(e)	P=0.093
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		(e)	P=0.061
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	1/49 (2%)	2/50 (4%)	9/50 (18%)
Adjusted Rates (b)	2.9%	6.3%	21.4%
Terminal Rates (c)	1/34 (3%)	2/32 (6%)	9/42 (21%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.008	P=0.479	P=0.022
Incidental Tumor Tests (d)	P=0.008	P=0.479	P=0.022
Cochran-Armitage Trend Test (d)	P=0.003		
Fisher Exact Test (d)		P=0.508	P=0.009
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/48 (6%)	1/46 (2%)	1/46 (2%)
Adjusted Rates (b)	8.3%	3.3%	2.6%
Terminal Rates (c)	2/34 (6%)	1/30 (3%)	1/38 (3%)
Week of First Observation	93	104	104
Life Table Tests (d)	P=0.179N	P=0.345N	P=0.267N
Incidental Tumor Tests (d)	P=0.211N	P=0.340N	P=0.334N
Cochran-Armitage Trend Test (d)	P=0.214N		
Fisher Exact Test (d)		P=0.325N	P=0.325N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Harderian Gland: Adenoma			
Overall Rates (a)	3/49 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	8.8%	9.1%	2.4%
Terminal Rates (c)	3/34 (9%)	2/32 (6%)	1/42 (2%)
Week of First Observation	104	103	104
Life Table Tests (d)	P=0.177N	P=0.634	P=0.233N
Incidental Tumor Tests (d)	P=0.213N	P=0.639	P=0.233N
Cochran-Armitage Trend Test (d)	P=0.231N		
Fisher Exact Test (d)		P=0.651N	P=0.301N

(a) Number of tumor-bearing animals/number of animals examined at the site

(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality

(c) Observed tumor incidence at terminal kill

(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

(e) No P value is reported because no tumors were observed in the 25 mg/kg and vehicle control groups.

TABLE C4. HISTORICAL INCIDENCE OF RENAL TUBULAR CELL TUMORS IN MALE $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	No. Examined	No. of Tumors	Diagnosis
Historical Incidence at EG&G Mason Research Institute			
		(b) 1	Tubular cell adenoma
		(c) 1	Tubular cell adenocarcinoma
TOTAL	299	2 (0.7%)	
Overall Historical Incidence			
		3	Tubular cell adenoma
		2	Tubular cell adenocarcinoma
TOTAL	1,490	5 (0.3%)	

(a) Data as of August 30, 1985, for studies of at least 104 weeks. No more than one tumor has been observed in any vehicle control group.

(b) Observed in the *n*-butyl chloride study

(c) Observed in the 1,2-dichloropropane study

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Ulcer, NOS		3 (6%)	1 (2%)
Abscess, NOS			1 (2%)
Inflammation, chronic	1 (2%)		
*Subcutaneous tissue	(49)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	
Abscess, NOS		1 (2%)	
Infection, fungal			1 (2%)
RESPIRATORY SYSTEM			
#Lung/bronchus	(49)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Lung/bronchiole	(49)	(50)	(50)
Metaplasia, NOS	1 (2%)		3 (6%)
#Lung	(49)	(50)	(50)
Inflammation, interstitial			1 (2%)
Inflammation, chronic focal			1 (2%)
Reaction, foreign body	1 (2%)	1 (2%)	
Hyperplasia, epithelial			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
#Bone marrow	(49)	(45)	(50)
Hyperplasia, hematopoietic		1 (2%)	1 (2%)
Hyperplasia, neutrophilic	2 (4%)	2 (4%)	
#Spleen	(49)	(50)	(49)
Congestion, NOS	1 (2%)		2 (4%)
Depletion, lymphoid	1 (2%)		
Hyperplasia, lymphoid		3 (6%)	
Hematopoiesis	11 (22%)	9 (18%)	4 (8%)
#Splenic capsule	(49)	(50)	(49)
Fibrosis, focal	1 (2%)		
#Mesenteric lymph node	(44)	(47)	(45)
Congestion, NOS	13 (30%)	12 (26%)	10 (22%)
Inflammation, acute	1 (2%)		
Inflammation, chronic		1 (2%)	
Depletion, lymphoid	1 (2%)		1 (2%)
Hyperplasia, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#Brain	(49)	(50)	(50)
Embolus, bone marrow	1 (2%)		
*Pelvis	(49)	(50)	(50)
Periarteritis		1 (2%)	
#Mesenteric lymph node	(44)	(47)	(45)
Lymphangiectasis	4 (9%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#Heart	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
Calcification, focal			2 (4%)
#Kidney	(49)	(50)	(50)
Perivasculitis		2 (4%)	
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(49)	(50)
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal	4 (8%)	1 (2%)	
Fibrosis, focal	1 (2%)		
Calcification, focal	1 (2%)		
#Liver	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Inflammation, focal		1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic	3 (6%)	1 (2%)	
Necrosis, NOS	3 (6%)		
Necrosis, focal	1 (2%)	6 (12%)	3 (6%)
Metamorphosis, fatty	4 (8%)	8 (16%)	19 (38%)
Calcification, focal			1 (2%)
Focal cellular change		1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)		
Angiectasis			1 (2%)
#Liver/hepatocytes	(49)	(50)	(50)
Hyperplasia, focal		1 (2%)	1 (2%)
#Pancreas	(48)	(47)	(50)
Ectopia	1 (2%)		
Dilatation/ducts		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Necrosis, focal		1 (2%)	
Necrosis, fat		1 (2%)	
Atrophy, focal	1 (2%)		
#Pancreatic acinus	(48)	(47)	(50)
Hyperplasia, focal	1 (2%)	3 (6%)	4 (8%)
#Periesophageal tissue	(43)	(34)	(37)
Inflammation, NOS	1 (2%)		
#Stomach	(49)	(50)	(49)
Inflammation, acute	2 (4%)	1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic	1 (2%)		2 (4%)
Erosion	1 (2%)	2 (4%)	
Acanthosis	1 (2%)		
#Forestomach	(49)	(50)	(49)
Ulcer, NOS		2 (4%)	
Hyperkeratosis	1 (2%)	2 (4%)	1 (2%)
Acanthosis	1 (2%)		
#Jejunum	(49)	(50)	(50)
Ulcer, NOS	1 (2%)		
#Ileum	(49)	(50)	(50)
Hypertrophy, NOS			1 (2%)
*Rectum	(49)	(50)	(50)
Prolapse	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Cyst, NOS	1 (2%)	3 (6%)	1 (2%)
Glomerulonephritis, NOS	32 (65%)	35 (70%)	43 (86%)
Pyelonephritis, acute	1 (2%)		
Inflammation, acute		1 (2%)	
Inflammation, acute focal	1 (2%)		
Abscess, NOS	1 (2%)		
Inflammation, chronic focal		2 (4%)	
Scar			1 (2%)
Necrosis, NOS		1 (2%)	
Calcification, focal	2 (4%)	5 (10%)	8 (16%)
Cytomegaly		41 (82%)	47 (94%)
#Renal papilla	(49)	(50)	(50)
Necrosis, NOS	1 (2%)		
#Kidney/tubule	(49)	(50)	(50)
Cast, NOS		3 (6%)	4 (8%)
Nephrosis, NOS		1 (2%)	
Inclusion, nuclear		1 (2%)	2 (4%)
Dysplasia, NOS		4 (8%)	
Regeneration, NOS	11 (22%)	13 (26%)	15 (30%)
#Urinary bladder	(49)	(49)	(50)
Calculus, gross observation only	2 (4%)	1 (2%)	2 (4%)
Calculus, microscopic examination	6 (12%)	6 (12%)	6 (12%)
Inflammation, acute		1 (2%)	
Inflammation, chronic focal			1 (2%)
Hyperplasia, epithelial	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(48)	(45)	(48)
Congestion, NOS		1 (2%)	
#Anterior pituitary	(48)	(45)	(48)
Cyst, NOS		1 (2%)	2 (4%)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Adrenal/capsule	(48)	(46)	(46)
Hyperplasia, NOS	9 (19%)	1 (2%)	1 (2%)
#Adrenal cortex	(48)	(46)	(46)
Accessory structure	1 (2%)		
Cytomegaly	1 (2%)		
Hyperplasia, focal		1 (2%)	1 (2%)
#Adrenal medulla	(48)	(46)	(46)
Hyperplasia, NOS	2 (4%)		3 (7%)
#Thyroid	(48)	(44)	(49)
Follicular cyst, NOS	1 (2%)		
Hyperplasia, follicular cell		3 (7%)	5 (10%)
#Pancreatic islets	(48)	(47)	(50)
Hypertrophy, NOS		1 (2%)	
Hyperplasia, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Preputial gland	(49)	(50)	(50)
Dilatation, NOS			2 (4%)
Inflammation, acute	1 (2%)		
Abscess, NOS	1 (2%)		1 (2%)
Inflammation, acute/chronic	4 (8%)	1 (2%)	2 (4%)
#Prostate	(46)	(47)	(48)
Abscess, NOS	1 (2%)		
Inflammation, acute/chronic		1 (2%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
*Seminal vesicle	(49)	(50)	(50)
Dilatation, NOS	1 (2%)	1 (2%)	
Inflammation, acute	1 (2%)		
Fibrosis			1 (2%)
Atrophy, NOS		2 (4%)	1 (2%)
#Testis	(49)	(50)	(50)
Inflammation, acute focal	1 (2%)		
Adhesion, NOS		1 (2%)	
Atrophy, NOS			1 (2%)
Hypospermatogenesis	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, interstitial cell		1 (2%)	
#Testis/tubule	(49)	(50)	(50)
Degeneration, NOS		1 (2%)	
Atrophy, focal	1 (2%)	2 (4%)	7 (14%)
*Epididymis	(49)	(50)	(50)
Abscess, NOS		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
#Brain	(49)	(50)	(50)
Hemorrhage		2 (4%)	
Calcification, focal		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(49)	(50)	(50)
Inflammation, acute		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone/periosteum	(49)	(50)	(50)
Callus		1 (2%)	2 (4%)
Metaplasia, osseous	1 (2%)		
*Bone/lower extremity	(49)	(50)	(50)
Regeneration, NOS	2 (4%)		
*Synovial tissue	(49)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	2 (4%)	1 (2%)	
Pannus	1 (2%)		
Hyperplasia, NOS	2 (4%)	7 (14%)	
*Cartilage, NOS	(49)	(50)	(50)
Degeneration, NOS	2 (4%)	3 (6%)	
Hyperplasia, NOS	1 (2%)	1 (2%)	
*Tendon	(49)	(50)	(50)
Metaplasia, cartilaginous	8 (16%)		2 (4%)
Metaplasia, osseous		3 (6%)	
BODY CAVITIES			
*Thorax	(49)	(50)	(50)
Hemothorax		1 (2%)	
*Mediastinum	(49)	(50)	(50)
Abscess, NOS		1 (2%)	
Reaction, foreign body	1 (2%)		
*Abdominal cavity	(49)	(50)	(50)
Inflammation, NOS		1 (2%)	
Necrosis, fat		1 (2%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES (Continued)			
*Peritoneum	(49)	(50)	(50)
Inflammation, NOS		1 (2%)	
*Pleura	(49)	(50)	(50)
Inflammation, NOS	2 (4%)		
*Pericardium	(49)	(50)	(50)
Inflammation, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Congestion, NOS			1 (2%)
Inflammation, focal	1 (2%)		
Inflammation, acute focal	1 (2%)		
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	35 (71%)	30 (60%)	41 (82%)
Necrosis, focal			1 (2%)
Amyloidosis	1 (2%)		1 (2%)
Axilla			
Abscess, NOS		1	
Lower extremity			
Ankylosis	3		
Foot			
Ulcer, NOS		2	
Inflammation, chronic		1	
Gangrene, NOS		1	
Omentum			
Necrosis, fat	1	2	
SPECIAL MORPHOLOGY SUMMARY			
Animal missing/no necropsy	1		

---

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.

# Number of animals examined microscopically at this site

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

		PAGE
TABLE D1	SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	145
TABLE D2	INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	148
TABLE D3	ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	154
TABLE D4a	HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE	156
TABLE D4b	HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE	157
TABLE D5	SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE	158

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma		1 (2%)	
Neurofibrosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(48)	(50)
Hepatocellular carcinoma, metastatic	1 (2%)		1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma			1 (2%)
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		
Malignant lymphoma, lymphocytic type	7 (14%)	2 (4%)	2 (4%)
Malignant lymphoma, histiocytic type	2 (4%)	7 (14%)	
Malignant lymphoma, mixed type	7 (14%)	2 (4%)	3 (6%)
*Subcutaneous tissue	(50)	(50)	(50)
Mast cell tumor	1 (2%)		
#Spleen	(50)	(48)	(50)
Malignant lymphoma, histiocytic type			1 (2%)
Malignant lymphoma, mixed type			2 (4%)
CIRCULATORY SYSTEM			
#Spleen	(50)	(48)	(50)
Hemangiosarcoma, unclear primary or meta			1 (2%)
#Liver	(50)	(48)	(50)
Hemangioma		1 (2%)	1 (2%)
Hemangiosarcoma			2 (4%)
#Urinary bladder	(49)	(48)	(49)
Hemangioma			1 (2%)
#Uterus	(50)	(47)	(49)
Hemangioma	1 (2%)		1 (2%)
#Ovary	(47)	(46)	(46)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(48)	(50)
Hepatocellular adenoma	1 (2%)	13 (27%)	23 (46%)
Hepatocellular carcinoma	2 (4%)	5 (10%)	10 (20%)
#Forestomach	(50)	(49)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	
#Duodenum	(50)	(48)	(50)
Adenocarcinoma, NOS	1 (2%)		
URINARY SYSTEM			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(44)	(43)	(38)
Adenoma, NOS	17 (39%)	8 (19%)	3 (8%)
#Adrenal medulla	(49)	(44)	(48)
Pheochromocytoma		1 (2%)	1 (2%)
#Thyroid	(50)	(45)	(48)
Follicular cell adenoma	1 (2%)	2 (4%)	1 (2%)
#Parathyroid	(22)	(22)	(23)
Adenoma, NOS			1 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Acinar cell carcinoma	2 (4%)	1 (2%)	1 (2%)
#Uterus	(50)	(47)	(49)
Leiomyoma			1 (2%)
Endometrial stromal polyp	1 (2%)	1 (2%)	1 (2%)
#Uterus/endometrium	(50)	(47)	(49)
Adenocarcinoma, NOS	1 (2%)		
#Ovary	(47)	(46)	(46)
Granulosa cell tumor	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Osteosarcoma, metastatic		1 (2%)	
Shoulder			
Osteosarcoma			1
Tail			
Osteosarcoma			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	19	30	27
Moribund sacrifice	3	7	8
Terminal sacrifice	26	13	15
Dosing accident	2		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	34	30	35
Total primary tumors	50	50	62
Total animals with benign tumors	21	21	29
Total benign tumors	25	31	37
Total animals with malignant tumors	22	16	17
Total malignant tumors	23	19	24
Total animals with secondary tumors##	1	2	1
Total secondary tumors	1	2	1
Total animals with tumors uncertain-- benign or malignant	2		
Total uncertain tumors	2		
Total animals with tumors uncertain-- primary or metastatic			1
Total uncertain tumors			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
## Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: VEHICLE CONTROL

ANIMAL NUMBER	036	044	070	039	005	026	042	013	043	011	012	016	031	032	014	015	003	021	002	040	029	037	025	038	001
WEEKS ON STUDY	000	000	001	010	058	069	071	073	077	086	086	086	088	088	089	089	090	092	094	094	096	101	103	103	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+
Thymus	+	+	-	+	+	+	+	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	-	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
Esophagus	-	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X			
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	-	+	-	+	+	+	-	+	+	-	+	+	+	-	-	-	+	+	+	+	+	+	+
Adenoma, NOS																			X	X	X	X	X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	-	+	-	+	+	-	-	-	+	-	-	-	+	-	+	-	-	-	+	+	-	+	-	-
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	N	+	N	-	+	N	-
Acinar cell carcinoma															X					X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp									X																
Hemangioma																									
Ovary	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+
Granulosa cell tumor																									
Hemangioma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS					X																				
Malignant lymphoma, lymphocytic type													X											X	
Malignant lymphoma, histiocytic type								X																	
Malignant lymphoma, mixed type																		X			X		X		X

+ Tissue examined microscopically
- Required tissue not examined microscopically
X Tumor incidence
N Necropsy, no autolysis, no microscopic examination
S Animal missexed

No tissue information submitted
C Necropsy, no histology due to protocol
A Autolysis
M Animal missing
B No necropsy performed

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	004	006	007	008	009	010	017	018	019	022	023	024	027	028	030	033	034	035	041	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mast cell tumor																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																						X				1
Alveolar/bronchiolar adenoma													X													1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Hepatocellular carcinoma																					X	X				2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	44
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS												X														1
Large intestine	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS			X	X			X	X	X		X			X	X		X	X		X						17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma											X															1
Parathyroid	-	+	-	-	-	-	-	+	-	+	+	+	-	-	+	+	-	-	-	+	+	-	+	+	+	22
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	N	N	+	N	+	N	+	N	+	+	+	N	N	+	+	+	+	+	N	+	*50
Acinar cell carcinoma																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS														X												1
Endometrial stromal polyp																										1
Hemangioma							X																			1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Granulosa cell tumor																		X								1
Hemangioma		X																								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS												X														1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Malignant lymphoma, lymphocytic type					X							X					X	X		X						7
Malignant lymphoma, histiocytic type																								X		2
Malignant lymphoma, mixed type		X														X							X			7

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: LOW DOSE

ANIMAL NUMBER	022	024	033	010	030	031	003	005	029	027	041	004	006	048	043	019	046	014	039	009	021	026	049	018	013
WEEKS ON STUDY	050	051	059	060	060	060	062	063	064	065	067	069	069	070	072	077	079	080	081	082	082	083	083	084	085
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Fibrosarcoma, metastatic																									
Trachea	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	-	A	-	+	+	+	+	+	-	[illegible]	+	+	-	+	+	+	+	+	-	+	+	+	+	-	+
Spleen	-	A	+	+	+	+	+	+	+	[illegible]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	-	A	+	+	+	+	+	-	+	+	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+
Thymus	-	A	+	+	+	+	-	+	+	-	+	+	-	-	-	-	+	+	+	-	-	-	+	-	+
CIRCULATORY SYSTEM																									
Heart	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																						X			X
Hemangioma															X										
Bile duct	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
Gallbladder & common bile duct	N	N	+	+	+	N	N	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	-	N
Pancreas	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
Stomach	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	A	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-
Adenoma, NOS																								X	
Adrenal	-	A	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	-	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
Follicular cell adenoma																									
Parathyroid	-	A	-	-	+	-	+	-	+	+	-	-	-	+	-	-	-	+	-	-	-	+	+	-	-
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	N	+	N	N	N	N	N	N	N	N	+	N	N	N	+	N	N	+	N	N	N
Acinar cell carcinoma																						X			
Uterus	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	-	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma, metastatic													X												
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type																	X						X		
Malignant lymphoma, mixed type																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE
(Continued)

ANIMAL NUMBER	036	040	042	020	032	008	007	011	017	050	025	044	001	002	012	015	016	023	028	034	035	037	038	045	047	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	086	087	088	090	093	095	097	097	097	097	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma								X																		1
Neurofibrosarcoma										X																1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma																									X	2
Fibrosarcoma, metastatic								X																		1
Trachea	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	-	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Thymus	+	+	+	-	-	+	+	-	+	-	-	-	-	+	-	+	+	+	+	-	+	+	-	+	+	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma			X		X		X					X		X	X	X	X	X	X		X			X	X	13
Hepatocellular carcinoma								X	X				X													5
Hemangioma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	N	N	N	N	N	N	+	+	+	+	+	+	+	N	*50
Pancreas	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Esophagus	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	-	-	42
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma													X													1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenoma, NOS						X		X								X			X		X			X	X	8
Adrenal	-	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pheochromocytoma																						X				1
Thyroid	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma																				X	X					2
Parathyroid	+	-	+	-	-	+	-	-	+	+	-	+	-	+	-	+	+	+	+	+	-	-	+	+	-	22
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	N	N	N	+	+	N	N	+	N	+	+	+	+	+	N	+	N	+	+	+	N	*50
Acinar cell carcinoma																										1
Uterus	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
Endometrial stromal polyp					X																					1
Ovary	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS															X										X	2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma, metastatic																										1
Malignant lymphoma, lymphocytic type														X		X										2
Malignant lymphoma, histiocytic type	X	X				X			X								X									7
Malignant lymphoma, mixed type				X																X						2

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE: HIGH DOSE

ANIMAL NUMBER	025	034	042	041	043	044	032	033	001	035	040	022	039	036	037	024	019	005	020	016	021	023	027	003	026
WEEKS ON STUDY	040	043	043	047	050	052	055	058	059	059	059	061	061	062	063	064	066	075	075	079	079	079	080	086	086
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma			X																			X			
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, unclear primary or metastatic																									
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																								X	
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+
Thymus	−	+	−	−	−	−	+	−	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X				X		X			X		X
Hepatocellular carcinoma																								X	
Hemangioma																									
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	+	+	+	−	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Hemangioma																									
ENDOCRINE SYSTEM																									
Pituitary	+	−	−	+	+	+	+	−	−	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+
Adenoma, NOS				X																					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Follicular cell adenoma																									
Parathyroid	+	+	+	+	−	−	+	−	+	−	−	−	−	−	−	−	−	+	+	−	+	−	−	+	+
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Acinar cell carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																							X		
Endometrial stromal polyp																									
Hemangioma																									
Ovary	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																		X							
Malignant lymphoma, mixed type															X										
Shoulder, NOS																									
Osteosarcoma																									
Tail																									
Osteosarcoma																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE
(Continued)

ANIMAL NUMBER	029	004	010	006	021	031	018	046	011	047	007	008	009	012	013	014	015	017	028	030	038	045	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	090	094	094	095	098	099	100	101	102	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic										X																1
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma										X																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, unclear prim or meta	X																									1
Malignant lymphoma, histiocytic type																						X				1
Malignant lymphoma, mixed type																				X						2
Lymph nodes	+	+	+	+	+	+	+	+	-	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	43
Thymus	-	-	-	-	-	-	+	-	-	-	-	+	+	+	-	-	-	+	+	+	+	+	+	+	+	18
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X				X	X	X			X	X	X	X	X	X	X		X	X	X	X		X	X	X	23
Hepatocellular carcinoma			X	X		X		X		X						X	X			X		X				10
Hemangioma																								X		1
Hemangiosarcoma	X								X																	2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	N	+	N	+	+	N	+	+	+	N	N	+	+	+	N	+	N	N	+	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	-	+	+	+	+	+	+	+	+	+	+	-	-	+	-	-	-	+	-	+	+	+	+	+	+	40
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	-	+	+	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																						X				1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	-	-	+	+	+	-	+	+	+	+	38
Adenoma, NOS		X										X														3
Adrenal	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma			X																							1
Thyroid	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma		X																								1
Parathyroid	+	+	-	-	+	+	+	-	-	+	-	+	-	+	-	-	-	+	-	+	-	+	-	-	+	23
Adenoma, NOS																				X						1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	+	N	+	N	N	N	+	N	+	+	N	N	+	+	+	+	N	+	+	+	*50
Acinar cell carcinoma																		X								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma																										1
Endometrial stromal polyp																									X	1
Hemangioma																								X		1
Ovary	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																					X					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type							X																			2
Malignant lymphoma, mixed type																X									X	3
Shoulder, NOS																										
Osteosarcoma																						X				1
Tail																										
Osteosarcoma							X																			1

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	Vehicle Control	75 mg/kg	150 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	2/48 (4%)	3/50 (6%)
Adjusted Rates (b)	3.8%	10.1%	11.1%
Terminal Rates (c)	1/26 (4%)	1/13 (8%)	0/15 (0%)
Week of First Observation	105	69	43
Life Table Tests (d)	P=0.129	P=0.327	P=0.200
Incidental Tumor Tests (d)	P=0.244	P=0.451	P=0.306
Cochran-Armitage Trend Test (d)	P=0.223		
Fisher Exact Test (d)		P=0.485	P=0.309
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	7/50 (14%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	24.2%	15.4%	8.1%
Terminal Rates (c)	5/26 (19%)	2/13 (15%)	0/15 (0%)
Week of First Observation	88	105	75
Life Table Tests (d)	P=0.179N	P=0.337N	P=0.256N
Incidental Tumor Tests (d)	P=0.087N	P=0.229N	P=0.1[illegible]2N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.080N	P=0.080N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	6.1%	28.4%	6.7%
Terminal Rates (c)	1/26 (4%)	1/13 (8%)	1/15 (7%)
Week of First Observation	73	79	105
Life Table Tests (d)	P=0.505	P=0.021	P=0.655N
Incidental Tumor Tests (d)	P=0.479N	P=0.125	P=0.523N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.080	P=0.500N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	7/50 (14%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	23.5%	11.9%	25.1%
Terminal Rates (c)	4/26 (15%)	1/13 (8%)	3/15 (20%)
Week of First Observation	92	90	63
Life Table Tests (d)	P=0.512	P=0.311N	P=0.525
Incidental Tumor Tests (d)	P=0.476N	P=0.140N	P=0.536N
Cochran-Armitage Trend Test (d)	P=0.303N		
Fisher Exact Test (d)		P=0.080N	P=0.380N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	17/50 (34%)	11/50 (22%)	8/50 (16%)
Adjusted Rates (b)	50.2%	48.7%	36.9%
Terminal Rates (c)	10/26 (38%)	4/13 (31%)	4/15 (27%)
Week of First Observation	58	79	63
Life Table Tests (d)	P=0.288N	P=0.466	P=0.297N
Incidental Tumor Tests (d)	P=0.070N	P=0.220N	P=0.059N
Cochran-Armitage Trend Test (d)	P=0.023N		
Fisher Exact Test (d)		P=0.133N	P=0.032N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	7.7%	2.8%	21.7%
Terminal Rates (c)	2/26 (8%)	0/13 (0%)	2/15 (13%)
Week of First Observation	105	72	90
Life Table Tests (d)	P=0.109	P=0.676N	P=0.143
Incidental Tumor Tests (d)	P=0.170	P=0.549N	P=0.194
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.500N	P=0.339

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	1/50 (2%)	13/48 (27%)	23/50 (46%)
Adjusted Rates (b)	3.4%	75.2%	91.3%
Terminal Rates (c)	0/26 (0%)	9/13 (69%)	13/15 (87%)
Week of First Observation	101	88	62
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	2/50 (4%)	5/48 (10%)	10/50 (20%)
Adjusted Rates (b)	7.7%	23.3%	45.7%
Terminal Rates (c)	2/26 (8%)	1/13 (8%)	4/15 (27%)
Week of First Observation	105	83	86
Life Table Tests (d)	P=0.001	P=0.065	P=0.001
Incidental Tumor Tests (d)	P=0.003	P=0.172	P=0.006
Cochran-Armitage Trend Test (d)	P=0.009		
Fisher Exact Test (d)		P=0.201	P=0.014
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	18/48 (38%)	29/50 (58%)
Adjusted Rates (b)	10.9%	84.7%	100.0%
Terminal Rates (c)	2/26 (8%)	10/13 (77%)	15/15 (100%)
Week of First Observation	101	83	62
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Pituitary Gland: Adenoma			
Overall Rates (a)	17/44 (39%)	8/43 (19%)	3/38 (8%)
Adjusted Rates (b)	54.6%	46.7%	14.7%
Terminal Rates (c)	12/26 (46%)	5/13 (38%)	1/11 (9%)
Week of First Observation	94	84	47
Life Table Tests (d)	P=0.036N	P=0.459N	P=0.038N
Incidental Tumor Tests (d)	P=0.005N	P=0.158N	P=0.006N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.033N	P=0.001N

(a) Number of tumor-bearing animals/number of animals examined at the site

(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality

(c) Observed tumor incidence at terminal kill

(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE D4a. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE $B6C3F_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	7/39	0/39	7/39
1,2-Dichloropropane	7/38	2/38	9/38
Chlorodibromomethane	12/49	2/49	14/49
n-Butyl chloride	7/39	1/39	8/39
Bis(2-chloro-1-methylethyl)ether	4/40	0/40	4/40
n-Butyl chloride	12/43	2/43	14/43
TOTAL	49/248 (19.8%)	7/248 (2.8%)	56/248 (22.6%)
SD (b)	6.19%	2.32%	8.00%
Range (c)			
High	12/43	2/38	14/43
Low	4/40	0/40	4/40
Overall Historical Incidence			
TOTAL	(d) 237/1,324 (17.9%)	(e) 20/1,324 (1.5%)	(d,e) 257/1,324 (19.4%)
SD (b)	8.44%	2.79%	8.95%
Range (c)			
High	18/49	5/47	18/49
Low	2/44	0/49	2/44

(a) Data as of August 30, 1985, for studies of at least 104 weeks

(b) Standard deviation

(c) Range and SD are presented for groups of 35 or more animals.

(d) Includes 38 chromophobe adenomas and 1 acidophil adenoma

(e) Includes five adenocarcinomas, NOS, and one acidophil carcinoma

TABLE D4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls Adenoma	 Carcinoma	 Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	3/48	0/48	3/48
1,2-Dichloropropane	1/50	1/50	2/50
Chlorodibromomethane	2/50	4/50	6/50
n-Butyl chloride	8/50	1/50	9/50
Bis(2-chloro-1-methylethyl)ether	5/50	2/50	7/50
n-Butyl chloride	1/50	2/50	3/50
TOTAL	20/298 (6.7%)	10/298 (3.4%)	30/298 (10.1%)
SD (b)	5.46%	2.73%	5.48%
Range (c)			
High	8/50	4/50	9/50
Low	1/50	0/48	2/50
Overall Historical Incidence			
TOTAL	71/1,489 (4.8%)	46/1,489 (3.1%)	116/1,489 (7.8%)
SD (b)	4.29%	2.62%	5.56%
Range (c)			
High	9/50	5/50	(d) 14/50
Low	0/50	0/50	0/49

(a) Data as of August 30, 1985, for studies of at least 104 weeks

(b) Standard deviation

(c) Range and SD are presented for groups of 35 or more animals.

(d) Second highest: 9/50

TABLE D6. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#Lung/bronchiole	(50)	(48)	(50)
Metaplasia, NOS		1 (2%)	1 (2%)
#Lung	(50)	(48)	(50)
Aspiration, NOS			1 (2%)
Congestion, NOS			1 (2%)
Hemorrhage		2 (4%)	1 (2%)
Bronchopneumonia, NOS			3 (6%)
Inflammation, chronic	1 (2%)		
Histiocytosis	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis	3 (6%)	10 (20%)	2 (4%)
#Bone marrow	(48)	(46)	(47)
Fibrosis, focal	29 (60%)	18 (39%)	13 (28%)
Hemosiderosis		2 (4%)	1 (2%)
Hypoplasia, NOS			1 (2%)
Hyperplasia, hematopoietic	2 (4%)		
Hyperplasia, neutrophilic	5 (10%)	13 (28%)	10 (21%)
#Spleen	(50)	(48)	(50)
Congestion, NOS			4 (8%)
Necrosis, focal		1 (2%)	1 (2%)
Hemosiderosis		1 (2%)	
Atrophy, NOS			1 (2%)
Depletion, lymphoid		1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
Hematopoiesis	11 (22%)	12 (25%)	18 (36%)
#Mandibular lymph node	(46)	(39)	(43)
Congestion, NOS	1 (2%)		1 (2%)
Plasmacytosis			1 (2%)
Hyperplasia, plasma cell		1 (3%)	
Hyperplasia, lymphoid		1 (3%)	
#Mediastinal lymph node	(46)	(39)	(43)
Plasmacytosis	2 (4%)	2 (5%)	1 (2%)
#Mesenteric lymph node	(46)	(39)	(43)
Congestion, NOS	2 (4%)		
Inflammation, acute		1 (3%)	
#Renal lymph node	(46)	(39)	(43)
Inflammation, acute/chronic			1 (2%)
#Thymus	(33)	(28)	(16)
Plasma cell infiltrate		1 (4%)	
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis			1 (2%)
Perivasculitis	1 (2%)		
#Mesenteric lymph node	(46)	(39)	(43)
Lymphangiectasia	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#Lung	(50)	(48)	(50)
Perivasculitis		1 (2%)	1 (2%)
#Heart	(50)	(48)	(49)
Inflammation, focal		1 (2%)	
Inflammation, acute focal		1 (2%)	
Calcification, NOS	1 (2%)		
Calcification, focal	1 (2%)	1 (2%)	4 (8%)
#Myocardium	(50)	(48)	(49)
Degeneration, NOS	11 (22%)	6 (13%)	10 (20%)
#Cardiac valve	(50)	(48)	(49)
Calcification, NOS		1 (2%)	
*Coronary artery	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
#Omentum	(50)	(49)	(50)
Lymphangiectasis	1 (2%)		
#Kidney	(50)	(48)	(50)
Perivasculitis		1 (2%)	
#Urinary bladder	(49)	(48)	(49)
Perivasculitis			1 (2%)
#Thymus	(33)	(28)	(18)
Lymphangiectasis	1 (3%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(46)	(48)
Inflammation, chronic focal	1 (2%)	7 (15%)	3 (6%)
#Liver	(50)	(48)	(50)
Congestion, NOS			1 (2%)
Inflammation, acute focal		1 (2%)	
Abscess, NOS			3 (6%)
Inflammation, acute/chronic		1 (2%)	
Necrosis, NOS			4 (8%)
Necrosis, focal	2 (4%)	4 (8%)	7 (14%)
Metamorphosis, fatty	11 (22%)	16 (33%)	15 (30%)
Calcification, focal			1 (2%)
Focal cellular change			4 (8%)
#Hepatic capsule	(50)	(48)	(50)
Inflammation, NOS		1 (2%)	
#Liver/hepatocytes	(50)	(48)	(50)
Hyperplasia, focal		1 (2%)	3 (6%)
#Pancreas	(49)	(45)	(47)
Dilatation/ducts	2 (4%)		
Inflammation, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Atrophy, NOS	4 (8%)		
Atrophy, focal	2 (4%)		
#Pancreatic acinus	(49)	(45)	(47)
Hyperplasia, focal			2 (4%)
#Stomach	(50)	(49)	(50)
Ulcer, NOS	1 (2%)		1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		2 (4%)
Erosion			1 (2%)
#Glandular stomach	(50)	(49)	(50)
Ulcer, NOS	1 (2%)		
Erosion	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(50)	(49)	(50)
Abscess, NOS	2 (4%)		
Inflammation, chronic		1 (2%)	
Necrosis, focal	1 (2%)		
Hyperplasia, epithelial	1 (2%)		2 (4%)
Hyperplasia, basal cell	1 (2%)		
Hyperkeratosis	4 (8%)	1 (2%)	4 (8%)
#Ileum	(50)	(48)	(50)
Amyloidosis	1 (2%)		
*Rectum	(50)	(50)	(50)
Inflammation, acute			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(48)	(50)
Congestion, NOS		1 (2%)	3 (6%)
Glomerulonephritis, NOS	19 (38%)	11 (23%)	11 (22%)
Abscess, NOS		1 (2%)	
Inflammation, chronic focal		2 (4%)	1 (2%)
Nephrosis, NOS	3 (6%)	7 (15%)	4 (8%)
Nephrosis, cholemic			1 (2%)
Necrosis, focal		1 (2%)	
#Renal papilla	(50)	(48)	(50)
Necrosis, NOS		1 (2%)	
#Kidney/tubule	(50)	(48)	(50)
Necrosis, NOS			4 (8%)
Necrosis, focal		6 (13%)	
Inclusion, nuclear	1 (2%)	2 (4%)	
Regeneration, NOS			2 (4%)
#Kidney/pelvis	(50)	(48)	(50)
Inflammation, chronic		1 (2%)	
#Urinary bladder	(49)	(48)	(49)
Inflammation, chronic focal			2 (4%)
ENDOCRINE SYSTEM			
#Pituitary	(44)	(43)	(38)
Congestion, NOS		2 (5%)	
#Anterior pituitary	(44)	(43)	(38)
Hyperplasia, focal	10 (23%)	8 (19%)	5 (13%)
Vascularization		1 (2%)	
#Adrenal	(49)	(44)	(48)
Congestion, NOS	1 (2%)		
Inflammation, acute			1 (2%)
#Adrenal/capsule	(49)	(44)	(48)
Hyperplasia, NOS	1 (2%)	1 (2%)	
#Adrenal medulla	(49)	(44)	(48)
Hyperplasia, NOS			1 (2%)
#Thyroid	(50)	(45)	(48)
Inflammation, chronic focal	1 (2%)		
Hyperplasia, follicular cell	6 (12%)	18 (40%)	21 (44%)
#Pancreatic islets	(49)	(45)	(47)
Hyperplasia, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Lactation	1 (2%)	1 (2%)	
#Uterus	(50)	(47)	(49)
Dilatation, NOS	1 (2%)		5 (10%)
Pyometra	3 (6%)	4 (9%)	2 (4%)
Inflammation, acute	1 (2%)		1 (2%)

TABLE D6. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHANE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#Uterus (Continued)	(50)	(47)	(49)
Abscess, NOS			1 (2%)
Atrophy, NOS		1 (2%)	3 (6%)
#Uterus/endometrium	(50)	(47)	(49)
Inflammation, acute		3 (6%)	
Hyperplasia, NOS	2 (4%)		
Hyperplasia, cystic	24 (48%)	21 (45%)	13 (27%)
Metaplasia, squamous		1 (2%)	1 (2%)
#Tubo-ovarian combined site	(50)	(47)	(49)
Abscess, NOS	8 (16%)	19 (40%)	18 (37%)
#Ovary	(47)	(46)	(46)
Cyst, NOS	8 (17%)	1 (2%)	2 (4%)
Multiple cysts	1 (2%)		1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic			1 (2%)
Atrophy, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(48)	(49)	(50)
Inflammation, acute			1 (2%)
#Brain	(48)	(49)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, acute focal		1 (2%)	
SPECIAL SENSE ORGANS			
*Internal ear	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Synovial tissue	(50)	(50)	(50)
Hyperplasia, NOS			1 (2%)
*Tarsal joint	(50)	(50)	(50)
Inflammation, NOS			1 (2%)
Metaplasia, osseous			1 (2%)
BODY CAVITIES			
*Thorax	(50)	(50)	(50)
Hemothorax	1 (2%)		
*Thoracic cavity	(50)	(50)	(50)
Inflammation, acute			1 (2%)
*Mediastinum	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Inflammation, acute		2 (4%)	1 (2%)
*Pleural cavity	(50)	(50)	(50)
Empyema		1 (2%)	1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
*Pericardium	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF BROMODICHLOROMETHAEN (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS		2 (4%)	2 (4%)
Inflammation, focal	1 (2%)	4 (8%)	1 (2%)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, acute focal		1 (2%)	2 (4%)
Inflammation, chronic	2 (4%)	1 (2%)	
Inflammation, chronic focal	23 (46%)	15 (30%)	18 (36%)
Amyloidosis	2 (4%)	1 (2%)	
Calcification, focal		1 (2%)	1 (2%)
Omentum			
Necrosis, fat	2	1	1
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1	1	
Auto/necropsy/histo perf		1	

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* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.

# Number of animals examined microscopically at this site

APPENDIX E

GENETIC TOXICOLOGY OF BROMODICHLOROMETHANE

PAGE

TABLE E1 MUTAGENICITY OF BROMODICHLOROMETHANE IN *SALMONELLA TYPHIMURIUM* 164

TABLE E2 MUTAGENICITY OF BROMODICHLOROMETHANE IN MOUSE L5178Y LYMPHOMA CELLS 165

TABLE E3 INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY BROMODICHLOROMETHANE 166

TABLE E4 INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY BROMODICHLOROMETHANE 169

TABLE E1. MUTAGENICITY OF BROMODICHLOROMETHANE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	118 ± 4.5	143 ± 7.1	131 ± 14.3	116 ± 3.8	116 ± 10.4	132 ± 7.8
	10	98 ± 8.1	140 ± 15.3		114 ± 1.8	117 ± 6.8	160 ± 7.2
	33	91 ± 1.2	126 ± 12.2	146 ± 8.6	106 ± 14.7	120 ± 3.2	135 ± 19.3
	100	100 ± 5.2	106 ± 3.6	136 ± 7.2	122 ± 4.4	117 ± 14.8	125 ± 8.1
	333	91 ± 8.9	117 ± 4.7	127 ± 13.9	112 ± 18.5	108 ± 11.3	123 ± 8.4
	1,000	99 ± 5.8	114 ± 4.1	(c) 29 ± 29.3	108 ± 4.8	102 ± 2.8	(c) 26 ± 26.3
	3,333			Toxic			
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	417 ± 10.7	377 ± 8.7	683 ± 19.1	966 ± 42.3	439 ± 14.4	456 ± 24.3
TA1535	0	36 ± 3.2	18 ± 0.9	35 ± 5.0	17 ± 0.0	36 ± 8.6	27 ± 5.8
	10	23 ± 3.6	30 ± 4.0		32 ± 4.0	24 ± 4.6	22 ± 3.8
	33	15 ± 2.4	24 ± 3.8	20 ± 4.6	36 ± 2.5	22 ± 1.7	26 ± 7.8
	100	18 ± 0.6	28 ± 6.5	23 ± 4.3	32 ± 4.0	23 ± 3.3	22 ± 4.4
	333	16 ± 2.4	17 ± 1.5	17 ± 10.7	37 ± 3.7	20 ± 2.6	24 ± 5.8
	1,000	16 ± 1.7	(c) 5 ± 3.7	(c) 4 ± 4.3	29 ± 1.9	22 ± 4.0	(c) 9 ± 6.2
	3,333			(c) 0 ± 0.0			
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	476 ± 28.6	342 ± 42.1	314 ± 9.5	245 ± 10.7	324 ± 11.1	178 ± 24.1
TA1537	0	8 ± 0.7	5 ± 1.9	7 ± 3.1	5 ± 0.9	8 ± 2.6	6 ± 0.9
	10	9 ± 2.3	4 ± 0.9		7 ± 0.9	9 ± 0.3	6 ± 1.0
	33	6 ± 1.3	7 ± 1.5	8 ± 0.3	7 ± 2.9	6 ± 1.2	7 ± 2.8
	100	8 ± 0.7	4 ± 0.3	7 ± 0.7	4 ± 0.0	6 ± 0.9	5 ± 1.5
	333	7 ± 0.7	5 ± 0.0	9 ± 2.0	7 ± 1.3	8 ± 2.6	8 ± 2.6
	1,000	4 ± 1.0	5 ± 2.2	(c) 0 ± 0.0	(c) 0 ± 0.0	9 ± 3.6	9 ± 0.9
	3,333			Toxic			
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	151 ± 11.7	350 ± 41.7	319 ± 28.5	406 ± 11.5	292 ± 1.9	135 ± 8.7
TA98	0	26 ± 0.6	27 ± 1.0	36 ± 0.0	20 ± 3.6	44 ± 4.6	28 ± 2.3
	10	19 ± 5.3	23 ± 5.2		34 ± 1.2	27 ± 1.7	36 ± 4.0
	33	22 ± 3.2	22 ± 4.0	37 ± 4.6	28 ± 4.4	28 ± 2.1	28 ± 0.3
	100	21 ± 5.5	18 ± 1.5	34 ± 7.1	35 ± 2.7	29 ± 4.8	23 ± 2.5
	333	14 ± 2.4	18 ± 1.3	34 ± 5.4	29 ± 2.2	29 ± 5.2	26 ± 3.0
	1,000	16 ± 1.9	20 ± 2.8	(c) 0 ± 0.0	14 ± 14.0	27 ± 2.8	21 ± 4.3
	3,333			Toxic			
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	749 ± 43.9	575 ± 33.3	691 ± 134.3	764 ± 21.3	313 ± 4.1	326 ± 10.7

(a) Study performed at SRI International. The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (95% ethanol) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.

(b) Revertants are presented as mean ± standard error from three plates.

(c) Slight toxicity

(d) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE E2. MUTAGENICITY OF BROMODICHLOROMETHANE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
-S9					
Trial 1					
Dimethyl sulfoxide		77.0 ± 8.2	100.3 ± 7.3	75.0 ± 11.9	33.0 ± 4.9
Bromodichloromethane					
	15.6	66.5 ± 2.5	122.0 ± 2.0	82.5 ± 21.5	41.5 ± 9.5
	31.2	77.5 ± 5.5	113.5 ± 5.5	105.0 ± 2.0	45.5 ± 2.5
	62.5	84.5 ± 6.5	98.0 ± 8.0	87.0 ± 28.0	35.5 ± 13.5
	125	86.0 ± 5.0	81.0 ± 10.0	113.5 ± 3.5	44.0 ± 1.0
	250	76.5 ± 7.5	34.0 ± 1.0	107.5 ± 21.5	46.5 ± 4.5
	500	Lethal			
Methyl methanesulfonate					
	15	30.0 ± 6.0	12.5 ± 5.5	383.5 ± 25.5	(d) 444.0 ± 116.0
Trial 2					
Dimethyl sulfoxide		107.3 ± 2.8	99.8 ± 1.2	84.0 ± 6.2	26.3 ± 1.7
Bromodichloromethane					
	200	99.0 ± 6.0	81.0 ± 2.0	71.0 ± 4.0	24.0 ± 3.0
	250	84.0 ± 12.0	60.0 ± 1.0	66.0 ± 1.0	26.5 ± 3.5
	300	105	51	86	27
	350	71.5 ± 19.5	30.5 ± 2.5	65.0 ± 22.0	29.5 ± 2.5
	400	96.0 ± 14.0	20.0 ± 0.0	109.0 ± 3.0	38.5 ± 4.5
Methyl methanesulfonate					
	15	40.5 ± 0.5	26.5 ± 4.5	208.5 ± 43.5	(d) 172.5 ± 33.5
+S9 (e)					
Trial 1					
Dimethyl sulfoxide		66.3 ± 4.6	100.0 ± 3.5	176.5 ± 18.9	89.0 ± 6.5
Bromodichloromethane					
	180	61.0 ± 2.0	68.0 ± 1.0	270.5 ± 28.5	(d) 147.5 ± 11.5
	240	50.5 ± 9.5	28.5 ± 5.5	244.0 ± 11.0	(d) 165.0 ± 24.0
	300	53.0 ± 7.0	22.0 ± 7.0	319.0 ± 72.0	(d) 210.5 ± 72.5
	360	53.5 ± 2.5	9.5 ± 0.5	430.5 ± 28.5	(d) 270.5 ± 29.5
	420	35.0 ± 4.0	4.0 ± 0.0	810.0 ± 55.0	(d) 798.0 ± 147.0
	480	Lethal			
Methylcholanthrene					
	2.5	27.0 ± 1.0	20.5 ± 1.5	770.5 ± 20.5	(d) 960.5 ± 7.5

TABLE E2. MUTAGENICITY OF BROMODICHLOROMETHANE IN MOUSE L5178Y LYMPHOMA CELLS (a,b) (Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
+S9 (e) (Continued)					
Trial 2					
Dimethyl sulfoxide		109.3 ± 1.2	100.0 ± 6.1	91.0 ± 5.8	27.7 ± 1.8
Bromodichloromethane					
	180	101.0 ± 0.0	48.0 ± 8.0	120.0 ± 13.0	39.5 ± 4.5
	240	79	39	100	42
	300	103.5 ± 8.5	31.0 ± 5.0	145.5 ± 10.5	(d) 46.5 ± 0.5
	360	96.5 ± 8.5	20.5 ± 0.5	144.0 ± 33.0	(d) 49.0 ± 7.0
	420	95.5 ± 3.5	9.5 ± 0.5	217.5 ± 1.5	(d) 76.5 ± 3.5
	480	Lethal			
Methylcholanthrene					
	2.5	85.0 ± 4.0	49.5 ± 0.5	673.0 ± 7.0	(d) 266.5 ± 15.5

(a) Study performed at Inveresk Research International. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). Indepth explanations and mathematical derivations of assay characteristics are presented by Myhr et al. (1985). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate; the average for the three tests is presented in the table. Cells (6×10^5 /ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error of replicate trials for approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

(e) Tests conducted with metabolic activation were performed as described in (a) except that S9 prepared from the liver of Aroclor 1254-induced F344 rats was added at the same time as the study chemical and/or solvent.

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY BROMODICHLOROMETHANE (a,b)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (c)
–S9 (d)								
Trial No. 1--Summary: Negative								
Dimethyl sulfoxide		50	1,035	467	0.45	9.3	26.5	
Bromodichloromethane	50	50	1,024	452	0.44	9.0	26.5	96.8
	160	50	1,038	471	0.45	9.4	26.5	101.1
	500	50	1,038	466	0.45	9.3	26.5	100.0
	1,600	0	(cytostatic)					
	5,000	0	(toxic)					
Mitomycin C	0.001	50	1,032	707	0.69	14.1	26.5	151.6
	0.010	50	1,028	2,520	2.45	50.4	26.5	541.9
Trial No. 2--Summary: Negative								
Dimethyl sulfoxide		50	1,046	439	0.42	8.8	26.0	
Bromodichloromethane	500	50	1,045	427	0.41	8.5	26.0	96.6
	1,000	50	1,047	516	0.49	10.3	26.0	117.0
	1,500	50	1,042	458	0.44	9.2	26.0	104.5
	2,000	50	1,040	518	0.50	10.4	26.0	118.2
	3,000	0	(cytostatic)				26.0	
	3,000	0	(cytostatic)				31.0	
	4,000	0	(toxic)					
Mitomycin C	0.001	50	1,046	1,402	1.34	28.0	26.0	318.2
	0.010	10	211	693	3.28	69.3	26.0	787.5
+S9 (e)								
Trial No. 1--Summary: Negative								
Dimethyl sulfoxide		50	1,047	470	0.45	9.4	26.0	
Bromodichloromethane	50	50	1,045	487	0.47	9.7	26.0	103.2
	160	50	1,038	496	0.48	9.9	26.0	105.3
	500	50	1,050	440	0.42	8.8	26.0	93.6
	1,600	50	1,047	499	0.48	10.0	26.0	106.4
	5,000	0	(cytostatic)					
Cyclophosphamide	0.300	50	1,037	595	0.57	11.9	26.0	126.6
	2	50	1,049	1,192	1.14	23.8	26.0	253.2
Trial No. 2--Summary: Questionable								
Dimethyl sulfoxide		50	1,042	426	0.41	8.5	26.0	
Bromodichloromethane	2,000	50	1,042	449	0.43	9.0	26.0	105.9
	3,000	50	1,043	445	0.43	8.9	26.0	104.7
	4,000	50	1,045	533	0.51	10.7	26.0	125.9
	5,000	50	1,038	511	0.49	10.2	26.0	120.0
Cyclophosphamide	0.300	50	1,043	667	0.64	13.3	26.0	156.5
	2	10	212	369	1.74	36.9	26.0	434.1

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY BROMODICHLOROMETHANE (Continued)

(a) Study performed at Environmental Health Research and Testing Laboratory. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (d) or (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.

(b) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.

(c) SCEs/cell of cultures exposed to study chemical relative to that of cultures exposed to solvent

(d) In the absence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.

(e) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY BROMODICHLOROMETHANE (a)

Trial 1					Trial 2				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b) Harvest time: 12.0 hours					**−S9 (b) Harvest time: 10.8 hours**				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	1	0.01	1		100	3	0.03	3
Bromodichloromethane					Bromodichloromethane				
160	100	3	0.03	3	250	100	4	0.04	4
500	100	3	0.03	2	500	100	2	0.02	2
1,600	100	4	0.04	3	1,000	100	3	0.03	3
5,000	100	1	0.01	1	2,000	100	1	0.01	1
Summary: Negative					Summary: Negative				
Mitomycin C					Mitomycin C				
0.250	100	45	0.45	32	0.250	100	24	0.24	22
1.000	100	60	0.60	45	1.000	50	39	0.78	42
+S9 (c) Harvest time: 13.0 hours					**+S9 (c) Harvest time: 13.0 hours**				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0.00	0		100	1	0.01	1
Bromodichloromethane					Bromodichloromethane				
160	100	0	0.00	0	250	100	0	0.00	0
500	100	3	0.03	2	500	100	3	0.03	3
1,600	100	1	0.01	1	1,000	100	1	0.01	1
5,000	100	0	0.00	0	2,000	100	1	0.01	1
Summary: Negative					Summary: Negative				
Cyclophosphamide					Cyclophosphamide				
15	100	11	0.11	9	15	100	32	0.32	28
50	100	37	0.37	31	50	50	42	0.84	46

(a) Study performed at Environmental Health Research and Testing Laboratory. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) or (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

(b) In the absence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.

(c) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX F

SENTINEL ANIMAL PROGRAM

PAGE

TABLE F1 MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE 173

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F_1 mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	*M. pul.* (*Mycoplasma pulmonis*)

II. Results

Results are presented in Table F1.

TABLE F1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF BROMODICHLOROMETHANE (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
MALE RATS		
6	5/5	Sendai
	2/5	RCV
12	5/5	Sendai
18	--	None positive
24	1/3	*M. pul.*
FEMALE RATS		
6	5/5	RCV
	5/5	Sendai
12	5/5	Sendai
18	4/5	Sendai
	3/5	RCV
24	2/5	Sendai
MALE MICE		
6	4/5	Sendai
12	--	None positive
18	5/5	MHV
24	3/5	MHV
FEMALE MICE		
6	1/5	Sendai
12	1/5	Sendai
18	5/5	MHV
24	4/5	Sendai
	3/5	MHV

(a) Blood samples were taken from sentinel animals at 6, 12 and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX G

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Meal Diet: May 1980 to May 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

		PAGE
TABLE G1	INGREDIENTS OF NIH 07 RAT AND MOUSE RATION	176
TABLE G2	VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION	176
TABLE G3	NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION	177
TABLE G4	CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION	179

TABLE G1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NIH, 1978; NCI, 1976b
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione activity
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.06 ± 1.10	22.0-26.3	36
Crude fat (percent by weight)	4.94 ± 0.46	4.2-6.0	36
Crude fiber (percent by weight)	3.40 ± 0.37	2.8-4.3	36
Ash (percent by weight)	6.31 ± 1.16	5.97-7.27	36
Essential Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.213-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.275 ± 0.076	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamins (a)			
Vitamin A (IU/kg)	11,489 ± 2,627	7,200-22,000	36
Vitamin D (IU/kg)	6,300		2
α-Tocopherol (ppm)	37.6	31.1-44.0	4
Thiamine (ppm)	17.31 ± 4.2	7.3-26.0	(b) 35
Riboflavin (ppm)	6.9	6.1-7.4	4
Niacin (ppm)	75	65-85	4
Pantothenic acid (ppm)	30.2	29.8-30.5	4
Pyridoxine (ppm)	7.2	5.6-8.8	4
Folic acid (ppm)	2.1	1.8-2.4	4
Biotin (ppm)	0.24	0.21-0.27	4
Vitamin B_{12} (ppb)	12.8	10.6-15.0	4
Choline (ppm)	3,315	3,200-3,430	4
Minerals (a)			
Calcium (percent)	1.28 ± 0.17	0.81-1.53	36
Phosphorus (percent)	0.99 ± 0.07	0.84-1.10	36
Potassium (percent)	0.809	0.772-0.846	3
Chloride (percent)	0.557	0.479-0.635	4
Sodium (percent)	0.304	0.258-0.349	4
Magnesium (percent)	0.172	0.166-0.177	4
Sulfur (percent)	0.278	0.270-0.285	4
Iron (ppm)	418	409-426	4
Manganese (ppm)	90.8	86.0-95.5	4
Zinc (ppm)	55.1	54.2-56.0	4
Copper (ppm)	12.68	9.65-15.70	4
Iodine (ppm)	2.58	1.52-3.64	4
Chromium (ppm)	1.86	1.79-1.93	4
Cobalt (ppm)	0.57	0.49-0.65	4

(a) Two to four batches of feed analyzed for nutrients reported in this table were manufactured during 1983 1985.

(b) One batch (7/22/81) was not analyzed for thiamine.

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.44 ± 0.17	0.13-0.93	36
Cadmium (ppm) (a)	0.10	0.40	36
Lead (ppm)	0.92 ± 0.65	0.33-2.93	36
Mercury (ppm) (b)	< 0.05	<0.05	26
Selenium (ppm)	0.29 ± 0.07	0.10-0.48	36
Aflatoxins (ppb) (b)	<5.0	<5-<10	36
Nitrate nitrogen (ppm) (c)	8.63 ± 4.61	<0.1-19.0	36
Nitrite nitrogen (ppm) (c)	1.86 ± 1.17	<0.1-5.3	36
BHA (ppm) (d)	4.52 ± 4.59	<1.0-20.0	36
BHT (ppm) (d)	2.99 ± 2.28	<1.0-13.0	36
Aerobic plate count (CFU/g)	132,583 ± 167,241	7,000-420,000	36
Coliform (MPN/g)	772.8 ± 910.7	<3.0->2,400	36
E. coli (MPN/g) (e)	6.43 ± 6.60	<3.0-23.0	35
E. coli (MPN/g) (f)	10.42 ± 24.80	<3.0-150.0	36
Total nitrosamines (ppb) (g,h)	5.75 ± 4.93	0.9-18.8	35
Total nitrosamines (ppb) (h,i)	11.22 ± 24.19	0.9-118.4	36
N-Nitrosodimethylamine (ppb) (h, j)	4.80 ± 4.75	0.9-16.0	35
N-Nitrosodimethylamine (ppb) (h,k)	10.37 ± 23.90	0.7-117.0	36
N-Nitrosopyrrolidine (ppb)	1.29 ± 0.63	<0.9-3.2	36
Pesticides (ppm)			
α-BHC (l)	<0.01		36
β-BHC (b)	<0.02		36
γ-BHC-Lindane (b)	<0.01		36
δ-BHC (b)	<0.01		36
Heptachlor (b)	<0.01		36
Aldrin (b)	<0.01		36
Heptachlor epoxide (b)	<0.01		36
DDE (a)	<0.01	0.05 (7/14/82)	36
DDD (b)	<0.01		36
DDT (b)	<0.01		36
HCB (b)	<0.01		36
Mirex (b)	<0.01		36
Methoxychlor (m)	<0.05	0.13 (4/26/82); 0.06 (6/24/82)	36
Dieldrin (b)	<0.01		36
Endrin (b)	<0.01		36
Telodrin (b)	<0.01		36
Chlordane (b)	<0.05		36
Toxaphene (b)	<0.1		36
Estimated PCBs (b)	<0.2		36
Ronnel (b)	<0.01		36
Ethion (b)	<0.02		36
Trithion (b)	<0.05		36
Diazinon (b)	<0.1		36
Methyl parathion (b)	<0.02		36
Ethyl parathion (b)	<0.02		36
Malathion (n)	0.08 ± 0.05	<0.05-0.25	36
Endosulfan I (o)	<0.01		36
Endosulfan II (o)	<0.01		36
Endosulfan sulfate (o)	<0.03		36

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) One observation was above the detection limit. The value obtained is listed under the range.
(b) All values were less than the detection limit, given in the table as the mean.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) Excludes one high value of 150/g obtained in the batch produced on 8/26/82.
(f) Mean, standard deviation, and range include the high value given in footnote e.
(g) Mean, standard deviation, and range exclude the high value of 118.4 ppb obtained for the batch produced on 4/27/81.
(h) All values were corrected for percent recovery.
(i) Mean, standard deviation, and range include the high value given in footnote g.
(j) Mean, standard deviation, and range exclude the high value of 117.0 ppb obtained for the batch produced on 4/27/81.
(k) Mean, standard deviation, and range include the value given in footnote j.
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) Two observations were above the detection limit. The values and the dates they were obtained are listed under the range.
(n) Thirteen batches contained more than 0.05 ppm.
(o) Eighteen batches produced during 5/20/80-11/25/81 were not analyzed for endosulfan I, endosulfan II, and endosulfan sulfate.

APPENDIX H

DATA AUDIT SUMMARY

APPENDIX H. DATA AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year toxicology and carcinogenesis studies of bromodichloromethane in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations of the Food and Drug Administration (implemented by the NTP beginning on October 1, 1981). The laboratory experiments were conducted for the NTP by EG&G Mason Research Institute, Worcester, Massachusetts, under a subcontract with Tracor Jitco, Inc. Animal dosing with bromodichloromethane began in June 1980 and ended in May 1983. The retrospective audit was conducted at the NTP Archives in February and March 1986 by the following personnel from Program Resources, Inc.: W. Oller, Ph.D. (Principal Investigator); K. Connor; J. Kovach, B.A.; S. Corson, H.T. (ASCP); K. Pace, B.S.; and J.R. Wright, B.S. The following individuals from Veritas Laboratories, Inc., also were involved in the audit: J. Sagartz, D.V.M., A.C.V.P.; and N. MacLachlan, D.V.M., A.C.V.P. F. Voelker, D.V.M., A.C.V.P., Pathology Associates, Inc., performed a 100% examination of the wet tissues for uncut lesions and trimmed, embedded, and sectioned the additional lesions found. S. Eustis, NTP, D.V.M., Ph.D., A.C.V.P., read and diagnosed these additional lesions.

The full report of the audit is on file at the NIEHS. The audit included, as minimum requirements, a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All chemistry records.
(3) Body weight and clinical observation data for a random 10% sample of the study animals.
(4) All inlife records concerning environmental conditions, masses, mortality, and animal identification.
(5) All postmortem records for individual animals concerning identification, disposition codes, condition codes, and correlation between gross observations and microscopic diagnosis.
(6) Wet tissues from a random 10% sample of the study animals to check for animal identification and the presence of untrimmed lesions.
(7) Slides and blocks of tissues from all vehicle control and high dose animals to examine for proper match and inventory.
(8) Tabulated pathology diagnoses for a random 10% of study animals to verify computer data entry.

The audit showed that the data in the Technical Report (including inlife observations and chemistry data) reflect the data at the NTP Archives. Uncut lesions in the wet tissues were found which were due in part to failure to open and examine the large intestines completely. As a result of this finding, all wet tissues were examined for uncut lesions, and these lesions then were sectioned by an NTP pathology support contractor. NTP pathology staff diagnosed these additional lesions. The final tables include the additional lesions found and represent a complete examination of all tissues. This additional pathology did not change the interpretations of the studies but primarily increased the number of tumors found in dosed animals.

In three instances, the animal number in the wet tissue bags did not agree with the number on the bag, but there was no indication that animals had been interchanged. There were six animals (two rats and four mice) whose deaths were listed as natural but might have been attributed to gavage accident.

The audit findings were reviewed by NTP staff. In conclusion, the documents and materials at the NTP Archives support the data and conclusions presented in this Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-*p*-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl)phosphonium Sulfate and Tetrakis(hydroxymethyl)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
322	Phenylephrine Hydrochloride
325	Pentachloronitrobenzene
327	Xylenes (Mixed)

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